5,268,181 causes both treatment-limiting hepatotoxicity and increases in uric acid and/or glucose levels.

Kindly amend the above-identified application for U.S. patent as follows.

In the Claims:

Please amend claims 1 and 3 as follows:

(1)(AMENDED) In claim 1, line 2, kindly substitute --treatment-limiting hepatotoxicity and treatment-limiting elevations in uric acid or glucose levels or both-- for "drug-induced hepatotoxicity".

(3)(AMENDED) In claim 3, line 2, kindly substitute --treatment-limiting hepatotoxicity and treatment-limiting elevations in uric acid or glucose levels or both-- for "drug-induced hepatotoxicity".

Remarks

In the October 2, 1999 Office Action, the Examiner rejected previous claims 1-4 under 35 U.S.C. §102(b) as being anticipated by O'Neill, U.S. Patent Number 5,268,181. According to the Examiner

> The scope of applicant's claims, which recite a nicotinic acid formulation, read on the prior art. The claims are directed to a composition however no distinct formulation components are claimed which would possibly distinguish applicant's formulation over the prior art. The O'Neill et al. formulation would inherently meet the stair-stepped absorption profile of applicants, since the formulation claimed is the same.

Reconsideration of the above-identified application for U.S. patent is respectfully requested.

I. Amended claims 1-4

Amended claims 1-4 are drawn to treating hyperlipidemia with a nicotinic acid formulation which exhibits an unique *in vivo* stair-stepped absorption profile without causing treatment-limiting

hepatotoxicity or liver damage and without causing treatment-limiting elevations in uric acid levels or glucose levels or both. It is respectfully submittted that **amended claims 1-4** are clearly patentable over the references of record, including O'Neill et al., U.S. patent No. 5,208,181, for the reasons further developed hereinafter and, therefor, are in condition for immediate allowance.

II. Related applications

The above-identified application for U.S. patent is a continuation-in-part application of U.S. Patent Application, Serial No. 08/814,974, filed March 6, 1997 ("the Parent Application"), which is a continuation application of U.S. Patent Application, Serial No. 08/368,378, filed on January 14, 1995 ("the Grandparent Application"), which is a continuation-in-part of U.S. Patent Application, Serial No. 08/124,392, filed on September 20, 1993 ("the Great Grandparent Application").

III. The methods as claimed in the O'Neill Patent can cause hepatotoxicity and abnormal elevations in uric acid and glucose levels as evidenced by Slo-Niacin® and Dr. Straughn's Declaration

Submitted herewith in support of **Amended claims 1-4** and for consideration by Examiner Spear is a copy of Dr. Staughn's Declaration under 37 CFR §1.131 and §1.601 *et seq.* (hereinafter "Straughn Declaration"). See Attachment A. The original Staughn Declaration was filed with the Parent Application.

By way of background, Dr. Staughn has been involved in the field of pharmaceutical sciences, such as pharmacology, bioavailability, pharmacokinetics and drug assay methodology, for 23-plus years. Straughn Declaration, ¶3. Dr. Straughn has published over 60 publications in the field of pharmaceutical sciences. Straughn Declaration, ¶3. In addition, Dr. Straughn's current research projects involve, *inter alia*, evaluating the effect of food and drug absorption from the GI tract, defining dissolution specifications for gelatin capsules using acetaminophen as a marker, and determining *in vivo* flux of transdermal dosage systems. Straughn Declaration, ¶4. Dr. Straughn further declares that he is very familiar with the conduct of drug trials in human subjects having been the principal or co-principal investigator in over 100 studies, Straughn Declaration, ¶5, and his funding sources have included the National Cancer Institute, the Food and Drug Administration, the Tennessee Department of Public Health and Enviroment, and a variety of pharmaceutical companies. Straughn Declaration, ¶6.

As developed further hereinafter, Dr. Straughn is of the opinion that the method claims in the O'Neill Patent can induce treatment-limiting hepatotoxicity and elevations in uric acid levels or glucose levels or both, and declares among other things, that

> "[o]ther than the representation made by Upsher-Smith in the O'Neill Patent specification about hepatotoxicity, ***I am unaware of any objective evidence whatsoever that would establish clear and convincing support*** for the Examiner's asserted position that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the method claims in the O'Neill Patent, would inherently avoid inducing treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both." Straughn Declaration, ¶25. (emphasis added)

> "...it is my opinion that the objective evidence, of which I am aware, ***does not support*** the position that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the claims in the O'Neill Patent (Exhibit 13), ***would inherently avoid*** treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both, especially when (a) Upsher-Smith itself warns in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibit 4, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7) that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," (b) Gray et al. (Exhibit 8) report that hepatotoxicity and glucose elevations are associated with Slo-Niacin therapy, and (c) McKenney et al. (Exhibit 10) and Medical Sciences Bulletin (Exhibit 11) report that Slo-Niacin therapy is implicated in niacin-induced hepatotoxicity." Straughn Declaration, ¶25. (emphasis added)

> "It is therefore my opinion that the administration of the Slo-Niacin formulation once-a-day, in accordance with the claims in the O'Neill Patent (Exhibit 13), ***will not inevitably avoid*** side effects or treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both. Accordingly, it is my opinion that those skilled in the pharmaceutical sciences, including myself, ***would predict and expect*** that an appreciable number of people who take Slo-Niacin in an amount effective to lower serum lipids or a lipid component once-a-day, whether they take it in the morning or evening, will experience treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both." Straughn Declaration, ¶26. (emphasis added)

(A) The O'Neill and Evenstad Patents

As the Examiner knows, the O'Neill U.S. patent no. 5,208,181 was filed on June 29, 1992, and it issued on Dec. 7, 1993 (hereinafter "the O'Neill Patent"). It is assigned to Upsher-Smith Laboratories, Inc. The O'Neill Patent is a continuation-in-part of the Evenstad Patent. The single daily dose method claimed in the O'Neill Patent is neither disclosed nor claimed in the Evenstad Patent. A copy is submitted with the Straughn Declaration, Exhibit 13.

As discussed at the October 28th Interview, the Evenstad U.S. patent no. 5,126,145 was filed on on June 11, 1990, and it issued on June 30, 1992 (hereinafter "the Evenstad Patent"). It is believed to be assigned to Upsher-Smith Laboratories, Inc. The Evenstad Patent is a continuation of U.S. patent application, Serial No. 08/337,460, which was filed on April 13, 1989 and which is now abandoned. A copy is submitted with the Straughn Declaration, Exhibit 12.

(1) The O'Neill Patent is totally silent as to uric acid or glucose

Neither the specification nor the claims of the O'Neill Patent mention, discuss or refer to uric acid or glucose. In other words, the O'Neill Patent specification and claims are totally and completely silent as to uric acid or glucose. The O'Neill Patent specification and claims, therefore, fail to consider, mention or claim in any manner or context whatsoever uric acid or glucose.

(2) The O'Neill Patent also does not expressly claim "without hepatotoxicity"

Even though the O'Neill specification references "hepatotoxicity," the claims in the O'Neill Patent do not expressly claim a method of lowereing serum lipids or a lipid component "without causing treatment limiting hepatotoxicity."

(B) Upsher-Smith's Slo-Niacin® tablets

Slo-Niacin® tablets are polygel controlled-release nicotinic acid tablets, manufactured by Upsher-Smith under the Evenstad Patent, which are designed for oral administration. See Straughn Declaration, ¶7 and Exhibits 2-7.

Upsher-Smith declares to the world that Slo-Niacin® is patented under the O'Neill and Evenstad Patents. See Straughn Declaration, ¶24 and Exhibits 2-7. The formulation and use of the Slo-Niacin® tablets fall under the claims of both the the Evenstad Patent and O'Neill Patent, respectively, as advised in the Slo-Niacin® literature publishe by Upsher-Smith. See Straughn Declaration, ¶24 and Exhibits 2-7. More specifically, the Slo-Niacin® tablets fall squarely within the scope of the formulation-specific claims of the Evenstad Patent and the formulation-specific method claims of the O'Neill Patent. See Straughn Declaration, ¶24 and Exhibits 2-7.

(1) Slo-Niacin® is marketed only as a dietary supplement - it is not FDA approved

Notwithstanding the O'Neill Patent and its teachings concenring lipid-lowering therapy, Slo-Niacin® has been and still is marketed by Upsher-Smith only as an over-the-counter (hereinafter "OTC"), non-prescription product. Straughn Declaration, ¶8. More specifically, Slo-Niacin® is marketed by Upsher-Smith as only an OTC *dietary supplement* for single daily dosing in amounts of 500 mg or less per day. Straughn Declaration, ¶8 and Exhibits 2-7. Slo-Niacin® tablets are available in 750mg, 500mg and 250mg strengths. Straughn Declaration, ¶8 and Exhibits 2-7.

Slo-Niacin® is not and has never been approved by the FDA for any purpose whatsoever, including dyslipidemia or for lowering serum lipids or lipid components, as claimed in the O'Neill Patent. See Straughn Declaration, ¶9.

Slo-Niacin® is not and has never been an FDA approved prescription drug. Thus, Upsher-Smith has marketed and sold and continues to market and sell Slo-Niacin® as only an OTC *dietary supplement*. Straughn Declaration, ¶10. Upsher-Smith does not market Slo-Niacin® for lowering serum lipids or a lipid component, Straughn Declaration, ¶10, and is prohibited from doing so under federal law.

The fact that Upsher-Smith markets Slo-Niacin® as only a *dietary supplement* to be used once-a-day at a dosage of 500 mg or less, or as directed by a physician can be easily confirmed:

(a) in the 1997 physicians' Desk Reference concerning Slo-Niacin® (hereinafter the "1997 PDR"), Straughn Declaration, Exhibit 2;

(b) in Upsher-Smith's Slo-Niacin® advertisement on the Internet at http://www.upsher-smith.com/sloniacin.html (hereinafter "Upsher-Smith's Internet Advertisement"), Straughn Declaration, Exhibit 3;

(c) by the labels utilized by Upsher-Smith on its 750mg, 500mg and 250mg Slo-Niacin® OTC products (hereinafter individually or collectively "Upsher-Smith's OTC Labels"), Straughn Declaration, Exhibits 4, 5 and 6, respectively; and

(d) by the package insert utilized by Upsher-Smith with its 750mg, 500mg and 250mg Slo-Niacin® OTC products (hereinafter "Upsher-Smith's Package Insert"), Straughn Declaration, Exhibit 7.

It is clear that Upsher-Smith instructs adults to take Slo-Niacin® as only an OTC dietary supplement, or as directed by a physician. Straughn Declaration, ¶12, Exhibits 2-7. It is also clear that Upsher-Smith neither instructs nor suggests to anyone to take Slo-Niacin® for dyslipidemia or for lowering serum lipids or lipid components, Straughn Declaration, ¶12, Exhibits 2-7, for such instruction would violate federal law.

(2) Upsher-Smith voluntarily warns adults that Slo-Niaicn® can cause hepatotoxicity and abnormal elevations in uric acid and glucose levels

According to the Commission Report concerning the safety of dietary supplements, as recited on page 23633 in the Federal Register, Vol. 63, No. 82, Wednseday, April 29, 1998 under Notices, of which a copy is attached herewith as Attachment E, the Commision Report notes that

> "...there is no mandatory requirement for industry, consumers, or health care professionals *to report adverse events resulting from consumption of foods and dietary supplements*, and specifically states that the Commisssion is not recommending such a requirement. However,...[t]he Commission Report strongly suggests that dietary supplement manufacturers include appropriate warning statements in product information where necessary." (emphasis added)

Thus, there is no federal requirement or law that requires Upsher-Smith to report adverse events concerning the use of OTC Slo-Niacin®. Notwithstanding, *Upsher-Smith voluntarily reports* in its own Slo-Niacin® literature and on Slo-Niacin® OTC product labels that adults taking niaicn in daily doses of 500 mg or more during the morning or night may experience (i) increases in uric acid and glucose levels, and (ii) abnormal liver function tests. See Straughn Declaration, Exhibits 2-7.

It is respectfully submitted that the purpose of reporting such adverse events concerning the use of Slo-Niacin® by Upsher-Smith is clear and cannot be ignored. *The reason Upsher-Smith warns about such unwanted side effects is clear-- because they can happen when taking Slo-Niacin® in doses of 500 mg or more once-per-day during the morning or night, whether as a dietary supplement or for any other purpose whatsoever!*

(3) Slo-Niacin® is taken only once-a-day in doses of only 500mg or less

Upsher-Smith instructs adults to take Slo-Niacin® only once-a-day in the morning or evening at a dosage of 500 mg or less, or as directed by a physician. Straughn Declaration, ¶13, Exhibits 2-7. More particularly, Upsher-Smith instructs adults to take Slo-Niacin® as follows:

250mg - one Slo-Niacin® tablet morning or evening, or as directed by a physician;

500mg - one Slo-Niacin® tablet morning or evening, or as directed by a physician;

and

750mg - one-half Slo-Niacin® tablet morning or evening, or as directed by a physician. Straughn Declaration, ¶13, Exhibits 2-7. It is clear thatUpsher-Smith does not instruct anyone to take daily doses of Slo-Niacin® in an amount greater than 500mg. Rather, Upsher-Smith relies upon physicians for such instruction.

(4) Upsher-Smith warns adults in its Slo-Niacin® literature that taking niacin once-a-day in doses of only 500mg or less can cause increases in uric acid and glucose levels and abnormal liver function tests

Upsher-Smith clearly warns adults in all Slo-Niaicn® materials that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin." Straughn Declaration, ¶14, Exhibits 2-7.

(5) Upsher-Smith suggest to adults that taking Slo-Niacin® once-a-day in doses of only 500mg or less can cause increases in uric acid and glucose levels and abnormal liver function tests

It is Dr. Sraughn's opinion, that Upsher-Smith has clearly inferred to adults in its literature that, if they take Slo-Niacin® once-a-day in the morning or evening in dosages of 500mg or greater, they may experience hepatotoxicity and elevations in uric acid levels or glucose levels or both. Straughn Declaration, ¶15, Exhibits 2-7.

Dr. Straughn's opinion is consistent with Upsher-Smith's own warnings. Straughn Declaration, ¶15, Exhibits 2-7

(6) Gray *et al.* report that Slo-Niacin® has caused increases in glucose levels and hepatotoxicity

In 1994, Gray et al. conducted a retrospective cohort study concerning the efficacy and safety of Slo-Niacin® in dyslipoproteinemic veterans at the Department of Veteran Affairs Medical Center, Long Beach, California. Straughn Declaration, ¶16 and Exhibit 8. According to Gray et al., it reports that data was collected and analyzed for 896 patients treated with Slo-Niacin® during a 36 month period. Straughn Declaration, ¶16 and Exhibit 8. During that 36-month period, the average daily dose of Slo-Niacin® was approximately 1.5 grams with the final dose of about 1.67 grams.

Straughn Declaration, ¶16 and Exhibit 8. Gray et al. further report that approximately one-half (461 of 896) of the patients were still receiving Slo-Niacin® at the end of the survey period. Straughn Declaration, ¶16 and Exhibit 8. More importantly, however, Gray et al. report that, of the 435 patients no longer taking Slo-Niacin, 249 patients had 276 documented reasons for discontinuation, and that the primary documented reasons for discontinuation were adverse effects caused by Slo-Niacin®, of which 43 patients had increased blood glucose levels and 33 patients experienced increased hepatic enzyme levels. Straughn Declaration, ¶16 and Exhibit 8. Gray et al. further report that 46 patients taking Slo-Niacin® met the criteria for niacin-associated hepatotoxicity. Straughn Declaration, ¶16 and Exhibit 8.

While it is unclear in Gray et al. as to how the 896 patients were dosed daily with Slo-Niacin®, it is believed that these 896 patients were dosed twice-a-day with Slo-Niacin®, as opposed to once-a-day, in accordance with the recommended dosing schedule adopted by the Department of Veteran Affairs Medical Center, Long Beach, California, as reported in Wu et al.: *Am. J. Hosp. Pharm.*, 47: 2031-2034 (1990) (hereinafter "Wu et al."). Straughn Declaration, ¶17 and Exhibit 9. According to Wu et al., the patients at the Department of Veteran Affairs Medical Center, Long Beach, California, are slowly titrated with Slo-Niacin® over a six-week period to a therapeutic dose of 1.5 grams per day. Straughn Declaration, ¶17 and Exhibit 9. More particularly, Wu et al. report that patients are given 250mg twice daily for the first two weeks, 500mg twice daily for the second two weeks, and 750mg twice daily thereafter. Straughn Declaration, ¶17 and Exhibit 9.

(7) McKenney *et al.* and others Report that Slo-Niacin® has been implicated in niacin-induced hepatotoxicity

In an article by McKenney et al.: *JAMA*, 271(9):672-677 (1994), it reports on page 677 thereof that *many different SR [nicotinic acid] products with various release mechanisms, including* Nicobid from Rhone-Poulenc Rorer Pharmaceuticals, Inc., **Slo-Niacin® from Upsher-Smith**, Nature's Plus, Niatrol, Endur-Acin and generic products from Goldline, Rugby Laboratories, Rockville Center, and Major Pharmaceutical **have been implicated in niacin-induced hepatotoxicity**. Straughn Declaration, ¶18 and Exhibit 10.

In an article published in the Medical Sciences Bulletin, entitled *The Toxicity of Niacin* and published on the Internet at http://pharminfo.com/pubs/msb/niaicn.html, it confirms McKenney et al. and again reports that **a number of nicotinic acid products have been implicated in niacin-**

induced hepatotoxicity, including® Slo-Niacin from Upsher-Smith. Straughn Declaration, ¶19 and Exhibit 11.

While the Medical Sciences Bulletin reports that Slo-Niacin® is a prescription product, this representation is in error because, as stated hereinabove, Slo-Niacin® is not and has never been approved by the FDA for any purpose, and that Slo-Niacin is not and has never been an FDA approved prescription drug. Straughn Declaration, ¶19 and Exhibit 11.

(8) It would not be obvious or expected that the administration of once-a-day Slo-Niaicn® would inherently avoid hepatotoxicity or elevations in uric acid levels or glucose levels or both

Dr. Straughn's declares that it would not be obvious or expected that the administration of once-a-day Slo-Niacin®, either in the morning or at night, would inherently avoid side effects or changes in liver tests, uric acid levels or blood glucose levels that were evident from twice daily dosing. See Straughn Declaration, ¶20. In fact, it is Dr. Sraughn's opinion that quite the opposite would be predicted and expected and this is consistent with the warnings provided by Upsher-Smith. See Straughn Declaration, ¶20, Exhibits 2-7.

Moreover, Dr. Straughn declares that it is common knowledge in the pharmaceutical sciences that, if a drug induces side effects when it is administered in divided daily doses in a certain total daily dosage amount, the same drug will also induce such side effects when it is administered in that same total daily dosage amount, but as only a single daily dose. Straughn Declaration, ¶21. Dr. Straughn further declares that it is also common knowledge in the pharmaceutical sciences to divide a daily single dose into further multiple daily doses, e.g., go from once-daily dosing to twice-daily or three times-daily dosing, or to divide twice daily-dosing into four-daily doses, in order to avoid side effects attributable to the fewer daily doses. Straughn Declaration, ¶21.

In view of this common knowledge, Dr. Straughn declares that Slo-Niacin® can cause hepatotoxicity and elevations in glucose and uric acid levels when administered once-a-day, as it does when administered twice-a-day in an equal daily dosage amount. Straughn Declaration, ¶22, Exhibits 2-7 and 8-11. In addition to his own professional background and 23-plus years of experiences in the field of pharmaceutical science, Dr. Straughn basis his declaration upon the fact that:

(a) Upsher-Smith infers to adults in its Slo-Niacin® warnings that hepatotoxicity and elevations in uric acid levels and glucose levels can occur in adults taking Slo-Niacin® once-a-day in a dosage amount of 500mg or more, Straughn Declaration, Exhibits 2-7:

(b) the report in Gray et al. that Slo-Niacin® induces hepatotoxicity and elevations in glucose and uric acid levels when it is taken in a dosage amount of approximately 1500 mg, Straughn Declaration, Exhibit 8; and

(c) the reports in McKenney et al. and the Medical Sciences Bulletin that Slo-Niacin® is implicated in niacin-induced hepatotoxicity, Straughn Declaration, Exhibits 10 and 11. See Straughn Declaration, ¶22.

(9) No clear and convincing support that the adminstration of Slo-Niacin® Once-a-day would inherently avoid hepatotoxicity or abnormal elevations in uric acid levels or glucose levels or both

In the October 2, 1999 Office Action, the Examiner has asserted that "..The O'Neill et al. formulation would inherently meet the stair-stepped absorption profile of applicants, since the formulation claimed is the **same**" (emphasis added).

Applicant respectfully disagrees. Dr. Straughn also respectfully disagrees. The independent researchers, who have studied Slo-Niacin® also disagree. The formulations nor the functional characteristics, such as the stair-stepped absorption profiles, are ***not*** the same. The objective evidence submitted with Dr. Straughn's Declaration clearly establishes that the formulation claimed is not the same as the formulations in the O'Neill Patent.

Other than the self-serving representation made by Upsher-Smith in the O'Neill Patent specification about no hepatotoxicity, the objective evidence submitted with the Straughn Declaration contradicts such a self-serving statement made by Upsher-Smith. Moreover, such objective evidence is clearly overwhelming, and it clearly suggests otherwise. For example, Upsher-Smith warns those adults taking Slo-Niacin® that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin." Straughn Declaration, Exhibits 2-7. Gray et al. report that hepatotoxicity and glucose elevations are associated with Slo-Niacin® therapy. McKenney et al. and Medical Sciences Bulletin report that Slo-Niacin® therapy is implicated in niacin-induced hepatotoxicity. Upsher-Smith voluntarily warns adults taking Slo-Niacin® about the possibility of experiencing hepatotoxicity and

abnormal elevations in uric acid levels and glucose levels when taking Slo-Niacin® as a dietary supplement, even though there is no legal labeling requirement with OTC products to do so. Slo-Niaicn® has never been approved by the FDA as being both safe and effective to lower serum lipids or lipid components or as a dietary supplement when administered once-a-day. Straughn Declaration, ¶9.

As declared by Dr. Straughn, he is unaware of any objective evidence whatsoever that would establish clear and convincing support for the position that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the method claims in the O'Neill Patent, would inherently avoid inducing treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both. Straughn Declaration, ¶25. Moreover, Dr. Straughn declares that the objective evidence, of which he is aware, does not support the position that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the claims in the O'Neill Patent, would inherently avoid treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both, especially when:

(a) Upsher-Smith warns in the 1997 PDR under Slo-Niacin® that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, Exhibit 2;

(b) Upsher-Smith warns adults in its Slo-Niacin® Internet Advertisement that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, Exhibit 3;

(c) Upsher-Smith warns adults on its OTC Slo-Niacin® labels that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, Exhibit 4, 5 and 6;

(d) Upsher-Smith warns adults in its OTC Slo-Niacin® package inserts that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, Exhibit 7;

(e) Gray et al. report that hepatotoxicity and glucose elevations are associated with Slo-Niacin® therapy, Straughn Declaration, Exhibit 8; and

(f) McKenney et al. and Medical Sciences Bulletin report that Slo-Niacin® therapy is implicated in niacin-induced hepatotoxicity, Straughn Declaration, Exhibits 10 and 11. See Straughn Declaration, ¶25.

(10) Slo-Niacin® will not inevitably avoid hepatotoxicity or abnormal elevations in uric acid levels or glucose levels or both - those skilled in the art would predict and expect that Slo-Niacin® will experience hepatotoxicity or abnormal elevations in uric acid levels or glucose levels or both

Also based upon the objective evidence submitted concerning Slo-Niaicn®, Dr. Straughn declares that it is his opinion that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the claims in the O'Neill Patent will not inevitably avoid side effects or treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both. See Straughn Declaration, ¶26. Accordingly, Dr. Straughn declares that, in his opinion, those skilled in the pharmaceutical sciences, including himself, would predict and expect that an appreciable number of people who take Slo-Niacin® in an amount effective to lower serum lipids or a lipid component once-a-day, whether they take it in the morning or evening, will experience treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both. See Straughn Declaration, ¶26.

VIII. Examiner cannot find that the functional Limitations in the Claims 1-4 are in Inherent in the O'Neill Patent

(A) Inherency

It is well settled patent law that inherency may **not** be established by probabilities or possibilities. *Binstead v. Littman*, 242 F.2d 1788 (BPAI 1986). The mere fact that a certain thing **may** result from a given set of circumstances is **not** sufficient. In re Oelrich, 666 F.2d 578, 581, 212 U.S.P.Q. 323 (CCPA 1981); Binstead v. Littman, 242 F.2d at1788.

With respect to the use of **inherency**, it is likewise settled patent law that

> "...where support must be based on an **inherent disclosure**, it is not sufficient that a person following the disclosure **might** obtain the result set forth in the counts; **it must inevitably happen**." (emphasis added)

Pinegree v. Hull, 518 F.2d 624, 627, 186 U.S.P.Q. 248 (CCPA 1975); *Dreyfus v. Sternau*, 357 F.2d 411, 414, 149 U.S.P.Q. 63 (CCPA 1966). See also *Snitzer v. Etzel*, 531 F.2d 1062, 1064, 189 U.S.P.Q. 415 (CCPA 1976).

Thus, lack of **clear** disclosure is **not** supplied by speculation as to what one skilled in the art **might do or might not do** if he followed the teaching of the patent specification. *Binstead v. Littman*, 242 F.2d 766, 769, 113 U.S.P.Q. 279 (CCPA 1957). The patent specification must be clearer than to suggest that one skilled in the art **might** construct a device or practice a method in a particular manner or **might** achieve a certain result if a device is constructed or a method is practiced in a particular manner. Binstead v. Littman, 242 F.2d at 769.

Accordingly, to **prove inherency,** it must be established that the necessary and only reasonable construction to be given to the supporting disclosure by one skilled in the art is one which will lend **clear and convincing support** to the inherent limitation in the interference count. *Langer v. Kaufman*, 654 F.2d 915, 918, 175 U.S.P.Q. 172 (CCPA 1972).

Moreover, it is well established patent law that, before a patent examiner can assert that a functional limitation may be an inherent characteristic, "...the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional[ity]... is an inherent charcteristic of the prior art [patent]." *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1788 (BPAI 1987).

(B) The Functional Limitations *" the stair-stepped absorption profile characterized by three separate phases" and "without causing treatment-limiting elevations in hepatotoxicity or uric acid levels or glucose levels or both"* are not Inherent to the O'Neill Patent Formulations

It is respectfully submitted that the O'Neill Patent formulations **do not** inherently exhibit the stair-stepped absorption profile characterized by three separate phases and **do not** avoid treatment-limiting hepatotoxicity or abnormal elevations in uric acid levels or glucose levels or both. It is respectfully submitted that the Examiner **cannot** establish that the necessary and only reasonable construction to be given to the O'Neill Patent by one skilled int the art is one which will lend clear and convincing support that O'Neill Patent formulations inherently exhibit the stair-stepped absorption profile characterized by three separate phases and avoid hepatotoxicity and abnormal elevations in uric acid levels or glucose levels or both, as claimed in pending **claims 1-4**.

Under U. S. patent law, it is not sufficient that such functional limitations might happen if one skilled in the art follows the O'Neill Patent; rather they must inevitably happen. There is no room for speculation or probabilities or possibilities as a means to establish inherency under U.S. patent law.

Turning now to **Amended claims 1-4**, which all include the positive functional limitations "exhibit the stair-stepped absorption profile characterized by three separate phases" and "without causing," the O'Neill Patent not only does not mention "stair-stepped absorption profiles" or uric acid" or "glucose" in any manner or context whatsoever, the O'Neill Patent is **dead silent** as to the terms "stair-stepped absorption profiles" or "uric acid" and "glucose." There is an obvious lack of any, never mind clear, disclosure in the O'Neill Patent for these terms. Clearly, the Examiner can only speculate, at best, that the O'Neill Patent formulations will "exhibit the stair-stepped absorption profile characterized by three separate phases" and will avoid "treatment-limiting hepatotoxicity and treatment-limitng elevations in uric acid levels or glucose levels or both", as claimed in pending **claims 1-4** and that one would be inheretly practicing the instantly claimed invention because the the formualtions of the O'Neill Patent are identical. This, however, neither supports nor establishes inherency. More importantly, the O'Neill formulations are **not** identical. It is therefor respectfully submitted that, based upon this lack of disclosure alone in the O'Neill Patent, the Examiners' inherency position as to "practicing the instantly claimed invention" **must** fail.

Turning now to a discussion of the objective evidence, as it applies to **amended claims 1-4**, it is clear that, when following the O'Neill Patent method claims, the functional limitations "without inducing treatment-limiting hepatotoxicity and treatment-limiting elevations in uric acid levels or glucose levels or both" do **not** inevitably happen. Straughn Declaration, ¶¶7-16, 18-20, 22, 25-26 and Exhibits 2-8 and 10-11. Rather, according to Dr. Straughn and the objective evidence submitted with Dr. Straughn's Declaration, just the opposite occurs. That is, one skilled in the art not only predicts, but expects to see hepatotoxicity and abnormal elevations in uric acid levels or glucose levels or both when following the O'Neill Patent claims, as evidenced by Slo-Niacin®. This prediction and expectation is true, notwithstanding the self-serving statement made by Upsher-Smith in the O'Neill Patent specification about "no hepatotoxicity." Dr. Straughn Declaration, ¶¶20, 22, 25 and 26.

Moreover, it is respectfully submitted that it is impossible to assert that the O'Neill Patent method claims will inherently avoid hepatotoxicity and/or abnormal elevations in uric acid levels or glucose levels or both, when:

(a) Upsher-Smith warns in the 1997 PDR under Slo-Niacin® that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, ¶14 and Exhibit 2;

(b) Upsher-Smith warns adults in its Slo-Niacin® Internet Advertisement that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, ¶14 and Exhibit 3;

(c) Upsher-Smith warns adults on its OTC Slo-Niacin® labels that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, Straughn Declaration, ¶14 and Exhibit 4, 5 and 6;

(d) Upsher-Smith warns adults in its OTC Slo-Niacin® package inserts that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," Straughn Declaration, ¶14 and Exhibit 7;

(e) Upsher-Smith warns and suggests to adults that "[i]ncreased uric acid and glucose levels and abnormal liver function tests" can result if you take Slo-Niaicn® in daily doses of 500mg or more of niacin, Straughn Declaration, ¶15 and Exhibits 2-7;

(f) Gray et al. report that hepatotoxicity and glucose elevations are associated with Slo-Niacin® therapy, Straughn Declaration, ¶16 and Exhibit 8;

(g) McKenney et al. and Medical Sciences Bulletin report that Slo-Niacin® therapy is implicated in niacin-induced hepatotoxicity, Straughn Declaration, ¶¶ 8-19 and 25 and Exhibits 10 and 11;

(h) Slo-Niaicn® has never been approved by the FDA for any purpose whatsoever, Straughn Declaration, ¶¶ 9-10;

(i) Those skilled in the art predict and expect that hepatotoxicity and abnormal elevations in uric acid levels or glucose levels or both can occur when taking Slo-Niacin® in daily doses of 500mg or more, Straughn Declaration, ¶¶ 20, 22 and 25-26; and

(j) Those skilled in the art are of the opinion that the administration of the Slo-Niacin® formulation once-a-day, in accordance with the claims in the O'Neill Patent, **will not inevitably avoid** side effects or treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both, and, **would predict and expect** that an appreciable number of people who take Slo-Niacin® in an amount effective to lower serum lipids or a lipid component once-a-day, whether they take it in the morning or evening, will experience treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both." Straughn Declaration, ¶26. (emphasis added)

It is respectfully submitted that, in view of the objective evidence submitted with and by Dr. Straughn's Declaration, one cannot adopt the position that, when following the O'Neill Patent method claims, as evidenced by the use of Slo-Niacin® once-a-day in a dosage of 500 mg or more, treatment-limiting hepatotoxicity and treatment-limiting elevations in uric acid levels or glucose levels or both will **not** inevitably happen. Moreover, it cannot be established or even asserted by the Examiner with any degree of reasonableness that the necessary and only reasonable construction to be given to the O'Neill Patent by one skilled in the art is ---- one which will lend *clear and convincing* support that the methods and formulations claimed by the O'Neill Patent can be practiced in a manner which will not cause elevations in the uric acid levels or glucose levels or both or hepatotoxicity to an extent which would require the methods claimed and formulations disclosed by the O'Neill Patent to be discontinued. At best, the Examiner can only speculate that the O'Neill Patent *might* suggest to one skilled in the art that the claimed methods and formulations of the O'Neill Patent, when used in a certain manner, *may* result in a treatment that does *not* cause elevations in the uric acid levels or glucose levels or both or hepatotoxicity to an extent which would require the methods claimed by the O'Neill Patent to be discontinued. Such results do *not* inevitably happen from the O'Neill Patent. Rather, the side effects are predicted and expected to happen by those of skill in this art, as evidenced by Dr. Straughn's Declaration. Consequently, any argument based upon inherency must therefore fail.

It is therefore respectfully submitted that the O'Neill Patent does not in any manner whatsoever disclose or suggest the functional limitation "stair-stepped absorption profiles" and "without causing hepatoxicity and elevations in the uric acid or glucose levels or both to an extent which would require the method or composition to be discontinued," as claimed in **amended claims 1-4**. It is therefore respectfully submitted that the functional limitations, as claimed in **claims 1-4** in the above-identified application for U.S. patent, are not inherent to the O'Neill Patent formulations.

IV. FDA Approval

In contrast to Slo-Niacin®, it has been respectfully point out at both the October 28th and August 18th Interviews that the FDA has substantiated the significance of Applicant's invention and these advantages. In July, 1997, the FDA approved Applicant's use of a sustained release ("SR") nicotinic acid product to treat mixed dyslipidemia in patients without causing drug-induced side

effects, e.g., treatment-limiting hepatotoxicity or elevations in glucose or uric acid levels. This FDA approval is a confirmation that Applicant's sustained release ("SR") nicotinic acid product and use thereof is both safe, i.e., without side-effects, and effective, i.e., providing a meaningful therapeutic improvement. The FDA's Notice of Approval for Kos Pharmaceutical, Inc.'s SR nicotinic acid product is submitted herewith as Attachment F.

It is respectfully submitted that the FDA, as of this date, has **never** approved "Slo-Niacin®," the sustained release nicotinic acid formulation covered by the claims of O'Neill et al., U.S. Patent No. 5,208,181, and Evenstad et al., U.S. Patent No. 5,126,141, and manufactured by Upsher-Smith Laboratories, Inc., Minneapolis, Minnesota.

V. Conclusion

It is respectfully submitted that all presently pending claims are patentably distinct over the disclosures of record when the disclosures are considered either alone or any appropriate combination. It is further respectfully submitted that all currently pending claims are in conformance with 35 U.S.C. §112. It is further respectfully submitted that the O'Neill Patent does not exhibit stair-stepped absorption profiles and inherently avoid treatment-limiting hepatotoxicity and elevations in uric acid levels or glucose levels or both, as cliamed in presently pending claims 1-4.

As a result of the foregoing amendments and remarks together with the accompanying documents, it is respectfully submitted that the present application and all pending claims are now in condition for allowance. Therefore, early passage of the above-reference application for U.S. patent to issuance is earnestly solicited.

Should the Examiner have any questions or require additional information or clarification, Applicant requests that the Examiner contact the attorney of record herein, Peter J. Manso, at the phone numbers noted below.

Respectfully Submitted,

Peter J. Manso
Reg. No. 32,264

March 18, 1999

Jenkens & Gilchrist, P.C.
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#6
4/14/99

November 13, 1998

PATENT

Attorney Docket No. 32892.00032

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	David J. Bova
Serial No.:	08/814,974
Filing Date:	March 6, 1997
Group Art Unit:	1502
Examiner:	J. Venkat R. Schwartz, Biotechnology Practice Specialist
Title:	METHODS AND SUSTAINED RELEASE NICOTINIC ACID COMPOSITIONS FOR TREATING HYPERLIPIDEMIA AT NIGHT

Assistant Commissioner of Patents
Washington, D.C. 20231

Dear Sir:

DECLARATION UNDER 37 CFR §1.131 and §§1.601 *et seq.*

I, Arthur B. Straughn, Pharm. D., hereby state and declare that:

1. I received my B.S. degree in pharmacy from the University of North Carolina in 1972 and my Doctor of Pharmacy from the University of Tennessee in 1974. My *curriculum vitae* is submitted herewith as Exhibit 1.

2. I am a Professor and Clinical Director of the Drug Research Laboratory in the Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, Memphis, Tennessee.

3. I have been on the faculty at the College of Pharmacy, University of Tennessee, Memphis, Tennessee, for 23-plus years where my teaching, research interests and over 60

publications are in the field of the pharmaceutical sciences, such as pharmacology, bioavailability, pharmacokinetics and drug assay methodology.

4. My current research projects involve, *inter alia*, evaluating the effect of food on drug absorption from the GI tract, defining dissolution specifications for gelatin capsules using acetaminophen as a marker drug, and determining *in vivo* flux of transdermal dosage systems.

5. I am extremely familiar with the conduct of drug trials in human subjects having been the principal or co-principal investigator in over 100 studies.

6. My funding sources have included the National Cancer Institute, the Food and Drug Administration (hereinafter the "FDA"), the Tennessee Department of Public Health and Environment, and a variety of pharmaceutical companies.

7. It is my understanding that Upsher-Smith Laboratories, Inc., Minneapolis, Minnesota, (hereinafter "Upsher-Smith") manufactures and sells "Slo-Niacin," a sustained release nicotinic acid formulation, which is in tablet form and designed for oral administration.

8. It is my understanding that Slo-Niacin is marketed by Upsher-Smith only as an over-the-counter (hereinafter "OTC"), non-prescription product. More specifically, it is my understanding that Slo-Niacin is marketed by Upsher-Smith as only an OTC *dietary supplement* for single daily dosing in amounts of 500 mg or less per day, and that the Slo-Niacin tablets are available in 750mg, 500mg and 250mg strengths.

9. It is my understanding that Slo-Niacin is not and has never been approved by the FDA for any purpose, including dyslipidemia or for lowering serum lipids or lipid components.

10. It is also my understanding that Slo-Niacin is not and has never been an FDA approved prescription drug. It is my understanding that Slo-Niacin is marketed and sold as only an OTC *dietary supplement*.

11. My understanding that Upsher-Smith markets Slo-Niacin as only a *dietary supplement* to be used once-a-day at a dosage of 500 mg or less, or as directed by a physician, is confirmed in (a) the 1997 physicians' Desk Reference (hereinafter the "1997 PDR") under Slo-Niacin product information at page 2767, of which a copy is submitted herewith as Exhibit 2, (b) in Upsher-Smith's advertisement on the Internet at http://www.upsher-smith.com/sloniacin.html (hereinafter "Upsher-Smith's Internet Advertisement"), of which a copy is submitted herewith as Exhibit 3, (c) by the

labels utilized by Upsher-Smith on its 750mg, 500mg and 250mg Slo-Niacin OTC products (hereinafter individually or collectively "Upsher-Smith's OTC Labels"), of which copies are submitted herewith as Exhibits 4, 5 and 6, respectively, and (d) by the package insert utilized by Upsher-Smith with its 750mg, 500mg and 250mg Slo-Niacin OTC products (hereinafter "Upsher-Smith's Package Insert"), of which a copy is submitted herewith as Exhibit 7.

12. Upon my review of the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit ?), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6), and Upsher-Smith's Package Insert (Exhibit 7), it is my opinion that Upsher-Smith instructs adults to take Slo-Niacin as only an OTC dietary supplement, or as directed by a physician. It is my opinion that Upsher-Smith neither instructs nor suggests to anyone, in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6) or Upsher-Smith's Package Insert (Exhibit 7), to take Slo-Niacin for dyslipidemia or for lowering serum lipids or lipid components.

13. According to the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7), Upsher-Smith instructs adults to take Slo-Niacin only once-a-day in the morning or evening at a dosage of 500 mg or less, or as directed by a physician. More particularly, and according to the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7), Upsher-Smith instructs adults to take Slo-Niacin as follows: 250mg - one Slo-Niacin tablet morning or evening, or as directed by a physician; 500mg - one Slo-Niacin tablet morning or evening, or as directed by a physician; 750mg - one-half Slo-Niacin tablet morning or evening, or as directed by a physician.

14. It is my understanding that Upsher-Smith warns adults in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6), and Upsher-Smith's Package Insert (Exhibit 7), that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin." See the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3) Upsher-Smith OTC Labels (Exhibits 4, 5 and 6), the and Upsher-Smith's Package Insert (Exhibit 7).

15. Based upon my 23-plus years experience in the field of the pharmaceutical sciences, and my review and understanding of Upsher-Smith's warnings made in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith OTC Labels (Exhibit 4, 5 and 6), and Upsher-Smith's Package Insert (Exhibit 7), it is my opinion that Upsher-Smith has inferred to adults that, if they take Slo-Niacin once-a-day in the morning or evening in dosages of 500mg or greater, they may experience hepatotoxicity and elevations in uric acid levels or glucose levels or both.

16. In 1994, Gray et al. conducted a retrospective cohort study concerning the efficacy and safety of Slo-Niacin in dyslipoproteinemic veterans at the Department of Veteran Affairs Medical Center, Long Beach, California. This study was reported at Gray et al.: *Annals of Internal Medicine*, 121(3):252-258 (1994), of which a copy is submitted herewith as Exhibit 8 (hereinafter "Gray et al."). I have read and I am familiar with Gray et al. and the study reported therein. According to Gray et al., it reports that data was collected and analyzed for 896 patients treated with Slo-Niacin during a 36 month period. During that 36-month period, the average daily dose of Slo-Niacin was approximately 1.5 grams with the final dose of about 1.67 grams. Gray et al. further report that approximately one-half (461 of 896) of the patients were still receiving Slo-Niacin at the end of the survey period. More importantly, however, Gray et al. report that, of the 435 patients no longer taking Slo-Niacin, 249 patients had 276 documented reasons for discontinuation, and that the primary documented reasons for discontinuation were adverse effects caused by Slo-Niacin, of which 43 patients had increased blood glucose levels and 33 patients experienced increased hepatic enzyme levels. Gray et al. further report that 46 patients taking Slo-Niacin met the criteria for niacin-associated hepatotoxicity.

17. While it is unclear in Gray et al. as to how the 896 patients were dosed daily with Slo-Niacin, it is inferred that these 896 patients were dosed twice-a-day with Slo-Niacin, as opposed to once-a-day, in accordance with the recommended dosing schedule adopted by the Department of Veteran Affairs Medical Center, Long Beach, California, as reported in Wu et al.: *Am. J. Hosp. Pharm.*, 47: 2031-2034 (1990), of which a copy is submitted herewith as Exhibit 9 (hereinafter "Wu et al."). According to Wu et al., the patients at the Department of Veteran Affairs Medical Center, Long Beach, California, are slowly titrated with Slo-Niacin over a six-week period to a therapeutic dose of 1.5 grams per day. More particularly, Wu et al. report that patients are given 250mg twice

daily for the first two weeks, 500mg twice daily for the second two weeks, and 750mg twice daily thereafter.

18. In an article by McKenney et al.: *JAMA*, 271(9):672-677 (1994), of which a copy is submitted herewith as Exhibit 10 (hereinafter "McKenney et al."), McKenney et al. report on page 677 thereof that many different SR [nicotinic acid] products with various release mechanisms, including Nicobid from Rhone-Poulenc Rorer Pharmaceuticals, Inc., Slo-Niacin from Upsher-Smith, Nature's Plus, Niatrol, Endur-Acin and generic products from Goldline, Rugby Laboratories, Rockville Center, and Major Pharmaceutical have been implicated in niacin-induced hepatitis.

19. In an article published in the Medical Sciences Bulletin, entitled *The Toxicity of Niacin* and published on the Internet at http://pharminfo.com/pubs/msb/niaicn.html, of which a copy is submitted herewith as Exhibit 11 (hereinafter "Medical Sciences Bulletin"), it confirms McKenney et al. and again reports that a number of nicotinic acid products have been implicated in niacin-induced hepatotoxicity, including *Slo-Niacin from Upsher-Smith*. While the Medical Sciences Bulletin (Exhibit 11) reports that Slo-Niacin is a prescription product, this representation is in error because, as stated hereinabove, it is my understanding that Slo-Niacin is not and has never been approved by the FDA for any purpose, and that Slo-Niacin is not and has never been an FDA approved prescription drug.

20. Based upon my 23-plus years experience in the field of the pharmaceutical sciences, it would not be obvious or expected that the administration of once-a-day Slo-Niacin, either in the morning or at night, would inherently avoid side effects or changes in liver tests, uric acid levels or blood glucose levels that were evident from twice daily dosing. In fact, it is my opinion that quite the opposite would be predicted and expected and this is consistent with the warnings provided by Upsher-Smith in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 2, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7).

21. In my opinion, it is common knowledge in the pharmaceutical sciences that, if a drug induces side effects when administered in divided daily doses in a certain total daily dosage amount, the drug will also induce such side effects when it is administered in that same total daily dosage amount, but as only a single daily dose. In my opinion, it is also common knowledge in the pharmaceutical sciences to divide a daily single dose into further multiple daily doses, e.g., go from once-daily dosing to twice-daily or three times-daily dosing, or to divide twice daily-dosing into four-daily doses in order to avoid side effects attributable to the fewer daily doses.

22. Thus, based upon my 23-plus years experience in the field of the pharmaceutical sciences and my review and understanding of (a) Upsher-Smith's warnings in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith OTC Labels (Exhibit 4, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7), (b) the report in Gray et al. (Exhibit 8) that Slo-Niacin causes hepatotoxicity and elevations in uric acid levels when administered twice-a-day in a total daily amount of 1500 mg, and (c) the reports by McKenney et al. (Exhibit 10) and the Medical Sciences Bulletin (Exhibit 11) that Slo-Niacin is implicated in niacin-induced hepatotoxicity, it is my opinion and belief that Slo-Niacin can cause hepatotoxicity and elevations in glucose and uric acid levels when administered once-a-day, as it does when administered twice-a-day in an equal dosage amount. In addition to my own professional background and experiences in the field of pharmaceutical science, my opinion is based upon the fact that (a) Upsher-Smith infers to adults in its warnings that hepatotoxicity and elevations in uric acid levels and glucose levels can occur in people taking Slo-Niacin once-a-day in a dosage amount of 500mg or more, (b) the report in Gray et al.(Exhibit 8) that Slo-Niacin induces hepatotoxicity and elevations in glucose and uric acid levels when it is taken twice-a-day in a dosage amount of approximately 1500 mg, and (c) the reports in McKenney et al.(Exhibit 10) and the Medical Sciences Bulletin (Exhibit 11) that Slo-Niacin is implicated in niacin-induced hepatotoxicity.

23. It is my understanding that the United States Patent Office issued two U.S. Patents to Upsher-Smith, namely, Evenstad et., U.S. Patent No. 5,126,145 (hereinafter the "Evenstad Patent"), of which a copy is submitted herewith as Exhibit 12, and O'Neill et al., U.S. Patent No. 5,268,181 (hereinafter the "O'Neill Patent"), of which a copy is submitted herewith as Exhibit 13. I have read and I am familiar with both the Evenstad Patent and the O'Neill Patent.

24. As I further understand it, the claims of the Evenstad Patent cover the Slo-Niacin formulation, and the claims of the O'Neill Patent (Exhibit 13) cover once-a-day use of the Slo-Niacin formulation for lowering serum lipids and lipid components. This is evident from the fact that Upsher-Smith has elected to patent mark its Slo-Niacin products with the Evenstad Patent Number, i.e., 5,126,145 or both the Evenstad Patent Number, i.e., 5,126,145 and the O'Neill, Patent Number, i.e., 5,268,181. See the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibits 4, 5 and 6), and Upsher-Smith's Package Insert (Exhibit 7).

25. It is my understanding that the Examiner has asserted that the administration of the Slo-Niacin formulation once-a-day, in accordance with the method claims in the O'Neill Patent

(Exhibit 13), would inherently avoid inducing treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both. I respectfully disagree. Other than the representation made by Upsher-Smith in the O'Neill Patent specification (Exhibit 13) about hepatotoxicity, I am unaware of any objective evidence whatsoever that would establish clear and convincing support for the Examiner's asserted position that the administration of the Slo-Niacin formulation once-a-day, in accordance with the method claims in the O'Neill Patent (Exhibit 13), would inherently avoid inducing treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both. Thus, it is my opinion that the objective evidence, of which I am aware, does not support the position that the administration of the Slo-Niacin formulation once-a-day, in accordance with the claims in the O'Neill Patent (Exhibit 13), would inherently avoid treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both, especially when (a) Upsher-Smith itself warns in the 1997 PDR (Exhibit 2), Upsher-Smith's Internet Advertisement (Exhibit 3), Upsher-Smith's OTC Labels (Exhibit 4, 5 and 6) and Upsher-Smith's Package Insert (Exhibit 7) that "[i]ncreased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500mg or more of niacin," (b) Gray et al. (Exhibit 8) report that hepatotoxicity and glucose elevations are associated with Slo-Niacin therapy, and (c) McKenney et al. (Exhibit 10) and Medical Sciences Bulletin (Exhibit 11) report that Slo-Niacin therapy is implicated in niacin-induced hepatotoxicity.

26. It is therefore my opinion that the administration of the Slo-Niacin formulation once-a-day, in accordance with the claims in the O'Neill Patent (Exhibit 13), will not inevitably avoid side effects or treatment-limiting hepatotoxicity or elevations in uric acid levels or glucose levels or both. Accordingly, it is my opinion that those skilled in the pharmaceutical sciences, including myself, would predict and expect that an appreciable number of people who take Slo-Niacin in an amount effective to lower serum lipids or a lipid component once-a-day, whether they take it in the morning or evening, will experience treatment-limiting hepatotoxicity and/or elevations in uric acid levels or glucose levels or both.

27. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11-14-98

By: _____
Arthur B. Straughn

att #5

CURRICULUM VITAE

April 28, 1998

NAME: ARTHUR BELKNAP STRAUGHN

DATE OF BIRTH: August 10, 1944

PLACE OF BIRTH: Durham, North Carolina

CITIZENSHIP: U.S.A.

MARITAL STATUS: Married August 31, 1968 in Knoxville, Tennessee

Spouse - Maiden Name:	Carol Jean Guthe
Date of Birth:	June 13, 1946
Place of Birth:	Chicago, Illinois
Education:	B.S., Human Ecology University of Tennessee M.S., Education Memphis State University

CHILDREN: Tate Lancelot, born February 18, 1977
Christopher Grant, born November 10, 1981

MILITARY SERVICE: U.S. Army 1966-1968
Inactive Reserve 1968-1972

EDUCATIONAL BACKGROUND:

Preparatory : Chapel Hill High School
Chapel Hill, North Carolina
Graduated 1962

Undergraduate : North Carolina State University
Raleigh, North Carolina

University of North Carolina
Chapel Hill, North Carolina
B.S. in Pharmacy, 1972

Post-Graduate : University of Tennessee
Center for the Health Sciences
Memphis, Tennessee
Pharm.D., 1974

EXHIBIT #1

Professional Experience:

United States Army	Surgery Assistant September 1966 - July 1968
North Carolina Memorial Hospital Department of Nursing Chapel Hill, North Carolina	Medication Assistant June 1971 - May 1972
Division of Pharmacy Practice School of Pharmacy University of North Carolina Chapel Hill, North Carolina	Instructor July 1972 - June 1973
Department of Medicinal Chemistry College of Pharmacy University of Tennessee Center for the Health Sciences Memphis, Tennessee	Assistant Professor July 1974 - June 1978
Department of Pharmaceutics College of Pharmacy University of Tennessee Center for the Health Sciences Memphis, Tennessee	Assistant Professor July 1978 - June 1979
Department of Pharmaceutics College of Pharmacy University of Tennessee Center for the Health Sciences Memphis, Tennessee	Associate Professor July 1979 - June 1985 With Tenure, July 1980
Depart. of Pharmaceutical Sciences College of Pharmacy University of Tennessee, Memphis Memphis, Tennessee	Professor and Clinical Director of the Drug Research Laboratory July 1985 - present Approved to Direct Ph.D. September, 1990

Course Currently Teaching at UT:

Pharmacokinetics (PHSC 211)
Pharmacokinetic Research Clerkship (PHSC 411)

Memberships in Societies and Associations

(1972-1979)	North Carolina Society of Hospital Pharmacists
(1973-1982)	American Society of Hospital Pharmacists
(1974-)	American Pharmaceutical Association
(1974-)	Rho Chi, National Pharmacy Honor Society
(1974-1979)	Associate Fellow - American College of Apothecaries
(1975-)	Memphis Area Society of Hospital Pharmacists
(1975-)	American Association of Colleges of Pharmacy
(1975-)	American Association for the Advancement of Science
(1981- 1987)	Academy of Pharmaceutical Sciences
(1982-)	American College of Clinical Pharmacy
(1984-)	Memphis-Shelby County Pharmaceutical Society
(1985-)	Sigma Xi
(1986-)	Drug Information Association
(1987-)	American Association of Pharmaceutical Scientists
(1989-)	Tennessee Pharmaceutical Association
(1992-)	Phi Lamda Sigma, National Pharmacy Leadership Society

Referee for:

Drug Intelligence and Clinical Pharmacy
American Journal of Hospital Pharmacy
Journal of Pharmaceutical Sciences
Journal of Pharmacokinetics and Biopharmaceutics
Clinical Pharmacy
Pharmaceutical Research
Pharmacotherapy

Reviewer for:

AMA Drug Evaluations

Student Extracurricular Activities:

Student APhA	1970-1972
Drug Abuse Education Committee	1970-1972

Consultantships:

Schering/Key Pharmaceuticals, Inc., Miami, FL
Cord Laboratories, Broomfield, CO
Glaxo Laboratories, Research Triangle Park, NC
Purdue Frederick Company, Norwalk, CT
DuPont Pharmaceuticals, Wilmington, DE
IDR, Inc., Gaithersbug, MD
ClinDAR, Inc., Durham, NC
Martec Pharmaceutical, Inc., Kansas City, MO
Kos Pharmaceuticals, Inc., Miami, FL
The Upjohn Co., Kalamazoo, MI
Pracon, Inc., Reston, VA
Harris Laboratories, Lincoln, NE
Seigfried Pharmaceuticas, Basel, Switzerland
Med. Ed., Inc., Hardford, CN
Carnrick Pharmaceuticals, NJ
Sano Corporation, Miami, FL
Timerx Technologies, Patterson, NY
Daniels Pharmaceuticals, St. Petersberg, FL
Kemic Research, Canada
Faulding Pharmaceuticals, Adalade, Australia

Honors and Awards: Teacher of the Year 1991 (Class of 1993)
Elected to Phi Lamda Sigma Pharmacy Leadership Society 1992
Student Goverment Association Excellence in Teaching Award 1993
Teacher of the Year 1993 (Class of 1995)
Teacher of the Year 1995 (Class of 1997)

Ancillary Appointments:

College of Pharmacy

Member, Task Force on Professional Practice (1976)
Member, U.T. Statewide Pharmacy Education Program Advisory Committee (1975-1977)
Member, Task Force on Student Cheating (1976)
Academic Student Advisor (1975-)
Member, Task Force on Student Clerkships (1976)
Member, Academic Standing and Promotion Review Committee (1976-1977)
Member, Faculty Advisory Council (1977-1983)
Member, Admissions Committee (1978-1980, 1988-1990)
Member, Curriculum Committee (1980-1985, 1990-1992)
Member, Search Committee for Pharmaceutics Chairman (1988-89)
Member, Search Committee for Clinical Pharmacy Chair (1990)
Director, Graduate Admissions in Pharmaceutics (1989-1993)
Member, Promotion and Tenure (1990-1994)
Member, Planning and Assessment (1993-1994)
Member, Technology Assessment (1993-)

UT, Memphis

Member, Faculty Senate (1977-1983, 1988-)
Chairman Budget and Benefits (1994-)
Faculty Senate Executive Council (1980-1982)
Graduate Faculty Level to Direct Students (1979-)
Member, Computer Committee (1981-1983)
Chairman, Governance & Credentials Committee (1981-1983)
Board of Directors, UTCHS Faculty Club (1981-1986)
Faculty Senate, Parliamentarian (1982-1983)
Member, Ad Hoc Committee on Faculty Evaluation (1983-1984)
Chairman, Membership Committee, UTCHS Faculty Club(1985-86)
Faculty Counselor to President Boling (1985-1987)
Member, Academic Information Advisory Committee (1988-92)
Chairman (1989-92)
Member, Institutial Review Board (1990-)
Member, UT Parking Authority (1991-)
Member, Ad Hoc Committee Graduate Reserach Council (1992-1993)
Member, UT Student Advisory Council (1993-1995)
Member, UT Campus Support Services (1996 -)

Research Project Director for the following Doctor of Pharmacy Candidates:

1. Steve K. Huffines
2. Charles D. Rutledge
3. David E. Stewart
4. John Fisher
5. James Eldridge
6. Leslie J. North
7. James F. Koren
8. Sharon Ternullo
9. E. Richard Kessler
10. Trevia Walton
11. Jane Miller
12. Greg Drexler
13. Mike Hayes
14. Dave DiPersio
15. Robert Henderson
16. David Butler
17. Diane Drain
18. Desouky F. Fayed
19. Timothy Mickle

Graduate Student Committees

1. Martin K.T. Yau, Pharmaceutics
2. E. Armstrong, Pharmacy Administration
3. R. Rackley, Pharmaceutics
4. V. Vashi, Pharmaceutics
5. Tina Ursic, Pharmacy Administration
6. Denise Ladd, Nursing
7. Reba Roberts, Pharmaceutics

Graduate Students Directed

_____1. Robbie Kidd

Publications:

1. "A Novel Pharmacokinetic Slide Rule for Dosage Computations", A. B. Straughn, Copyright 1974.

2. "Assurance of Drug Quality (Bioavailability)", J. H. Coleman and A. B. Straughn, Diseases of the Nervous System, 36:63 (1975).

3. "Warfarin Induced Hypoprothrombiremia: Potentiation of Hyperthyroidism", T. Self, M. Weisburst, E. Wooten, A. B. Straughn, and J. Oliver, J.A.M.A., 231:1165(1975).

4. "Effect of Hyperthyroidism on the Hypoprothrombinemic Response to Warfarin", T. H. Self, A. B. Straughn and M. R. Weisburst, Am. J. Hosp. Pharm., 33:387 (1976).

5. "Bioavailability of Eleven Sulfisoxazole Tablets", G. Slywka, A. P. Melikian, A. B. Sraughn and M. C. Meyer, J. Pharm. Sci., 33:387 (1976).

6. "Bioavailability of Eleven Phenytoin Products", A. P. Melikian, A. B. Straughn, G. W.A. Slywka, P. L. Whyatt and M. C. Meyer, J. Pharmacokin. Biopharm., 5:133 (1977).

7. "Drug Interactions Involving Aminosalicylic Acid", M. C. Meyer, T. H. Self and A. B. Straughn, Rev. Drug Interactions, 2:107 (1977).

8. "Estimations of Drug Dosing Regimens with a Pharmacokinetics Slide Rule", A. B. Straughn, C. A. Cruze and M. C. Meyer, Am. J. Hosp. Pharm., 34:197 (1977).

9. "Meprobamate Bioavailability Monograph", M. C. Meyer and A. B. Straughn, J.A.Ph.A., NS17:173 (1977).

10. "Digitalis Intoxication", C. E. Kossman, A. B. Straughn and B. O. McGraw, Tenn. Med. Assoc. J., September 1977, P. 644.

11. "Factors Affecting the Bioavailability of Chlorothiazide in Man", M. C. Meyer and A. B. Straughn, Curr. Ther. Res., 22:573 (1977).

12. "The Relative Bioavailability of Meprobamate Tablets in Man", M. C. Meyer, A. P. Melikian and A. B. Straughn, J. Pharm. Sci., 67:129 (1978).

13. "The Bioavailability of Sulfadiazine Solutions, Suspensions and Tablets in Man", M. C. Meyer, A. B. Straughn, G. Ramchander, J. C. Cavagnol and A. F. B. Mabadeje, J. Pharm. Sci., 67:1659 (1978).

14. "The Influence of Dosage Form on Papaverine Bioavailability", M. C Meyer, R. Gollamudi and A. B. Straughn, J. Clin. Pharmacol., 19:435 (1979).

15. "Simultaneous Determination of Methenamine and Formaldehyde in the Urine of Humans after Methenamine Administration", R. Gollamudi, M. C. Meyer and A. B. Straughn, Biopharm. Drug Dispos., 1:27 (1979).

16. "The Bioavailability of Chlorothiazide Tablets in Man", A. B. Straughn, A.P. Melikian and M. C. Meyer, J. Pharm. Sci., 68:1099 (1979).

17. "A Multiple-Dose Study of Sustained-Release Theophylline and Aminophylline", M. C. Meyer, A. B. Straughn and P. Lieberman, Chest, 78:300 (1980).

18. "Bioavailability of Microsize and Ultramicrosize Griseofulvin Products in Humans", A. B. Straughn, M. C. Meyer, G. Raghow and K. Rotenberg, J. Pharmacokin.Biopharm., 8:34 (1980).

Publications: (Cont.)

19. "Evaluation of Enzyme Immunoassay, Radioassay, and Radio-immunoassay of Serum Methotrexate, with Liquid Chromatography as a Standard", R. G. Buice, W. E. Evans, J. Karas, C. A. Nicholas III, P. Sidhu, A. B. Straughn, M. C. Meyer and W. R. Crom, Clin. Chem., 26:1902 (1980).

20. "Pharmacokinetics of Propylthiouracil Upon P. O. Administration in Man", H. P.Ringhand, W. A. Ritschel, M. C. Meyer, A.B. Straughn and T. Hardt, Intl. J. Clin. Pharmacol. Ther. Toxicol., 18:3011 (1980).

21. "Urinary Excretion of Methenamine and Formaldehyde: Evaluation of 10 Methenamine Products in Humans", R. Gollamudi, A. B. Straughn and M. C. Meyer, J. Pharm. Sci., 70:596 (1981).

22. "Chloramphenicol Clearance in Infants", G. J. Burckart, F. Barrett, A. B. Straughn, S. R. Ternallo, J. Clin. Pharm., 22:49 (1982).

23. "HPLC Determination of Benzthiazide in Biological Fluids", M. C. Meyer, P. Hwang, A. B. Straughn, K. Rotenberg, Biopharm. Drug Disposition, 3:1 (1982).

24. "Serious Bioavailability Problems With a Generic Prolonged Release Quinidine Gluconate Product", M. C. Meyer, A. B. Straughn, P. Lieberman, J. Jacob, J. Clin. Pharmacol., 22:131 (1982).

25. "Model-Independent Steady-State Volume of Distribution", A. B. Straughn, J. Pharm. Sci., 71:597 (1982).

26. "Serum Salicylate Concentrations Achieved by AspirinAdministered at Six and Twelve Hour Dosing Intervals", C. D. Butler and A. B. Straughn, Clinical Pharmacy, 1:458 (1982).

27. "Relative Bioavailability of Acetazolamide Tablets", A. B. Straughn, R. Gollamudi and M. C. Meyer, Biopharm. Drug Disposition, 3:75 (1982).

28. "Noneffect of Rifampin on Theophylline Disposition in Rabbits", T. H. Self, M. M. Self, J. P. Worden, W. S. Taylor and A. B. Straughn, Res. Comm. Chem.Path. Pharm.,32:921 (1982).

29. "Isoniazid-Induced Alterations in Theophylline Pharmacokintics", J. R. Thompson, G. J. Burckart, T. H. Self, R. E. Brown and A. B. Straughn, Curr. Ther. Res., 32:921(1982).

30. "Bioavailability of Propylthiouracil in Humans", H. P. Ringhand, W. A. Ritschel, M. C. Meyer A. B. Straughn and B. E. Cabana, J. Pharm. Sci., 72:1409 (1983).

31. "Absorption of Phenobarbital from Tablets and Elixir", M. C. Meyer, A. B. Straughn, G. Raghow, W. L. Schary and K. S. Rotenberg, J. Pharm. Sci., 73:485 (1984).

32. "Plasma Levels of Ethaverine After Oral Administration to Humans", M. C. Meyer, G. Raghow and A. B. Straughn, Biopharm. Drug Dispos., 4:401 (1983).

33. "Bioequivalence, Dose Proportionality and Pharmacokinetics of Naltrexone After Oral Administration", M. C. Meyer, A. B. Straughn, M. Lo, W. L. Schary, C. C. Whitney, J. Clin. Psychiatry, 45:15 (1984).

34. "Effect of Rifampin on Theophylline Disposition", A. B. Straughn, R. Henderson, P. Lieberman, T. H. Self, Ther. Drug Monitoring, 6:153 (1984).

35. "Administration of Theo-Dur Once-A-Day vs. Twice-A-Day," A. B. Straughn, M. C. Meyer, A. L. Golub, M. A. Gonzalez, In: Sustained Release Theophylline and Nocturnal Asthma,p. 116: Eds. A.F. Isls and P. von Wichert. Excerpta Medica, Amsterdam.

36. "A Chronopharmacokinetic Model for Sustained Release Formulation," A. B. Straughn, M. C. Meyer, A. L. Golub and M. A. Gonzalez, Annual Reviews of Chronopharmacology 1:92 (1985).

Publications: (Cont.)

37. "Bioavailability of Dyphylline and Dyphylline-Guiafenesin Tablets in Humans," A. B. Straughn, G. C. Wood, G. Raghow and M.C. Meyer, J. Pharm. Sci. 74:335 (1985).

38. "Comparison of High Pressure Liquid Chromatography and Fluorescence Polarization Immunoassay Methods in a Theophylline Pharmacokinetic Study," R. L. Lalonde, M. B. Bottorff and A. B. Straughn, Ther. Drug Monitoring, 7:442 (1985).

39. "Determination of Free Disopyramide Plasma Concentrations Using Ultrafiltration and EMIT," G. Raghow, M.C. Meyer and A.B. Straughn. Ther. Drug Monitoring, 7:467 (1985).

40. "Bioavailability of Seven Furosemide Tablets in Man," A. B. Straughn, G. C. Wood, G. Raghow, and M. C. Meyer, Biopharm. Drug Dispos. 7:113 (1986).

41. "Dialzability and Pharmacokinetics of Indomethacin in Adult Patients with End-Stage Renal Disease," V.A. Skoutakis, C. Carter, N.J. Wojciechowski, A.B. Straughn, and M.C. Meyer. Drug Intelligence and Clin. Pharm., 12:956 (1986).

42. "Comparison of High Pressure Liquid Chromatography and Fluorescence Polarization Immunoassay to Assess Quinidine Pharmacokinetics," M.B. Bottorff, R.L. LaLonde, and A.B. Straughn. Biopharm. Drug Dispos., 8:213 (1987).

43. "Effect of Food on Absorption of Cefuroxime Axetil," A.B. Straughn, D.A. Finn, and M.C. Meyer. Biopharm. Drug Dispos., 8:519 (1987).

44. "Influence of a Standard Meal on the Absorption of a Controlled-Release Pseudoephedrine Suspension," D.A. Graves, M.T. Wecker, M.C. Meyer, A.B. Straughn, L.P. Amsel, O.N. Hinsvark, A.E. Bhargava and K.S. Rotenberg. Biopharm. and Drug Dispos., 9:267 (1988).

45. "The Absorption of Sustained-Release Methylphenidate Formulations Compared to an Immediate-Release Formulation," K.S. Partick, A.B. Straughn, E.J. Jarvi, G.R. Breese and M.C. Meyer. Biopharm. and Drug Dispos. 10:165 (1989).

46. "A Circadian Rhythm in Theophylline Disposition During a Constant-Rate Intravenous Infusion of Aminophylline in the Dog," R.J. Rackley, M.C. Meyer and A.B. Straughn. J. Pharm. Sci. 77:658 (1988).

47. "Chronopharmacokinetic Simulation of a Circadian Rhythm in Theophylline Disposition During a Constant-Rate Intravenous Infusion of Aminophylline in the Dog," R.J. Rackley, A.B. Straughn and M.C. Meyer, Ann. Review of Chronopharmacology (1988).

48. "Gas Chromatographic-Mass Spectrometric Analysis of Plasma Oxybutynin Using a Deuterated Internal Standard," K.S. Partick, J.S. Markowitz, E.J. Jarvi and A.B. Straughn, M.C. Meyer, J. of Chromatogrtaphy 487:91 (1989).

49. "In Vitro and In Vivo Evaluation of Seven 50mg and 100mg Nitrofurantoin Tablets," M.C. Meyer, G.C. Wood and A.B. Straughn, Biopharm. and Drug Dispos. 10:321(1989).

50. "Gas Chromatographic-Mass Spectrometric Analysis of Plasma Nifedipine" K.S. Patrick, E.J. Jarvi, A.B. Straughn and M.C.Meyer, J. Chrom. (Biomed. App.) 495:123 1989)

51. "The Effect of Raising Gastric pH with Ranitidine on the Absorption and Elimination of Theophylline from a Sustained-Release Theophylline Tablet," C.J. Betlach, A.B. Straughn, M.C. Meyer, M. Bailer, V.I. Vashi, P. Lieberman and M.A. Gonzalez, Pharm. Res. 8:1512 (1991).

Publications: (Cont.)

52. "Circadian Rhythms in Theophylline Disposition: Simulations and Observations in the Dog," R.J. Rackley, M.C. Meyer and A.B. Straughn, J. Pharm. Sci. 50:835 (1991).

53. "Postmenopausal Steroid Replacement with Micronized Dehydroepiandrosterone (DHEA): Preliminary Oral Bioavailability and Dose Proportionality Studies," J.E. Buster, P.R. Casson, A.B. Straughn, et al, Am. J. Obstet. Gynecol. (in Press).

54. "The Bioinequivalence of Carbamazepine Tablets with a Historyof Clinical Failures," M.C. Meyer, A.B. Straughn, et al, Pharm. Res. 9:1612 (1992).

55. "Quantitative Detrmination of Cyclobenzaprine in Human Plasma by High Pressure Liquid Chromatography," P.T.R. Hwang, D.A.Young, A.B. Straughn, M.C. Meyer, J. Liquid Chrom. 16:1163(1993).

56. "The Effect of Gastric pH on the Absorption of Controlled-Release Theophylline forms in Humans," M.C. Meyer, A.B. Straughn, E.J. Jarvi, G.C. Wood, V.I. Vashi, P. Hepp, and J. Hunt, Pharm. Res. 10:1037(1993).

57. "Biopharmaceutical Factors in Seizure Control and Drug Toxicity," M.C. Meyer and A.B. Straughn, Am J. Hosp. Pharm. 50:S17 (1993).

58. "Comparative Steady-State Bioavailability of Theo-24 and Theo-Dur in Healthy Men," G. Cefali and A.B. Straughn, Ann. Allergy, 72:218 (1994).

59. "Oral Dehydroepiandrosterone in Physiologic Doses Modulates Immune Function in Postmenopausal Women," P.R. Casson, R.N. Andersen, H.G. Herrod, F.B. Stentz, A.B. Straughn, G.E. Abraham, and J.E. Buster, Am. J. Obstet. Gynecol., 169:1536 (1993).

60. "Effect of Meals and Dosage-Form Modification on Theophylline Bioavailability from a 24-Hour Sustained-Release Delivery System," M.A. Gonzalez and A.B. Straughn, Clinical Therapeutics, 16:804 (1994).

61. "Pharmacokinetic Comparison of a Once-Daily and Twice-Daily Theophylline Delivery System," M.A Gonzalez, J. Kisicki, and A.B. Struaghn, Clinical Therapeutics, 16:686 (1994).

62. "Replacement of Dehyroepiandrosterone Enhances T-Lymphocyte Insulin Binding in Postmenopausal Women," P.R. Casson, L.C. Faquin, F.B. Stentz, A.B. Straughn, R.N. Andersen, G.E. Abraham, and J.E. Buster, Fertility and Sterility 63:1027 (1995)

63. "'Pavlovian' Food Effect on the Enterohepatic Recirculation of Piroxicam," J.E. Polli, S. Bigora, D. A. Piscitelli, A.B. Straughn, and D. Young, Biopharm. Drug Disp. 17:635 (1996).

64. "Lack of In Vivo/In Vitro Correlations for 50 mg and 250 mg Primidone Tablets," M.C. Meyer, A. B. Straughn, R.M. Mhatre, V. Shah, R.L. Williams and L. Lesko, Pharm. Res. (in press).

Abstracts:

1. "Use of a Pharmacokinetic Slide Rule in Teaching Pharmacokinetics", AACP Annual Meeting, Minneapolis, MN, July, 1976.

2. "Effect of Hyperthyroidism on the Hypoprothrombinemic Response to Warfarin", American Pharmaceutical Association Annual Meeting, San Francisco, CA, October, 1975.

3. "Bioavailability of Eleven Sulfisoxazole Tablets", Academy of Pharmaceutical Sciences Annual Meeting, Atlanta, GA, November, 1975.

4. "Bioavailability of Eleven Diphenylhydantoin Capsules", Academy of Pharmaceutical Sciences Annual Meeting, Atlanta, GA, December, 1975.

5. "Bioavailability of Papaverine Dosage Forms", ASHP Mid-Year Meeting, Atlanta, GA, December, 1977.

6. "Bioavailability of Five Warfarin Products in Humans, ASHP Mid-Year Meeting, Las Vegas, NV, December, 1979.

7. "Steady-State Bioavailability of Two Sustained-Release Theophylline Preparations", ASHP Mid-Year Meeting, Las Vegas, NV, December, 1979.

8. "Effect of DOSS on the Absorption of Orally Administered Digoxin", ASHP Mid-Year Meeting, San Francisco, CA, December, 1980.

9. "Pharmacokinetic Analysis with Statistical Moments", ASHP Mid-Year Meeting, San Francisco, CA, December, 1980.

10. "Comparison of Six and Twelve Hour Dosing of Aspirin", ASHP Mid-Year Meeting, San Francisco, CA, December, 1980.

11. "In Vitro Predictors of Theophylline Bioavailability I: Correlations Between Fraction Dissolved and Fraction Absorbed", Academy of Pharmaceutical Sciences, Orlando, FL November, 1981.

12. "In Vitro Predictors of Theophylline Bioavailability II: Correlations with Statistical Moments", Academy of Pharmaceutical Sciences, Orlando, FL November, 1981.

13. "Hemoperfusion in Theophylline Toxicity", ASHP Mid-Year Meeting, New Orleans, LA, December, 1981.

14. "Pharmacokinetics of Ceftazidime in Normal Subjects and EndStage Renal Disease", Interscience Conference on Antimicrobial Agents and Chemotherapy", Miami Beach, FL October, 1982.

15. "Ceftazidime Pharmacokinetics During Continuous Ambulatory Peritoneal Dialysis (CAPD) and Intermittent Peritoneal Dialysis (IPD)", American College of Clinical Pharmacy, Washington, D.C., July, 1983.

16. "In Vitro Prediction of Steady-State Fluctuations in Theophylline Concentrations", American College of Clinical Pharmacy, Washington, D.C., July, 1983.

17. "A Chronopharmacokinetic Model for Sustained-Release Formulations", First International Montreaux Conference: Biological Rhythms and Medications, Montreaux, Switzerland, March, 1984.

18. "Disposition Kinetics of Controlled-Release Theophylline Dosed at 12 and 24 h Dosing Intervals", Academy of Pharmaceutical Sciences, Montreal, Canada, May, 1984.

19. "Bioavailability of Cefuroxime Axetil Administered After Food," Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., October, 1984.

Abstracts: (Cont.)

20. "Steady-State Aspirin and Metabolite Pharmacokinetics After Administration of Immediate and Controlled-Release Dosage Forms," American College of Clinical Pharmacy, Orlando, FL, July, 1985.

21. "Effect of Gastric pH on the Absorption of Theophylline from Sustained-Release Formulations," American Association of Pharmaceutical Scientists, Boston, MA, June, 1987.

22. "Chronopharmacokinetic Simulation of a Circadian Rhythm inTheophylline Disposition During a Constant-Rate Intravenous Infusion of Aminophylline in the Dog," Third International Conference of Chronopharmacology, Niece, France, March, 1988.

23. "Chronopharmacokinetics with Sustained-Release Theophylline,"Third International Conference on Chronopharmacology, Niece, France, March, 1988.

24. "Evidence for Circadian Change in Volume of Distribution of Theophylline in the Dog. American Association of Pharmaceutical Scientists, Orlando, FL Nov. 1989.

25. "High Fat Meal Effects on the Single Dose Pharmacokinetics of a new Once-a-Day Theophylline Tablet, 45th Annual Congress of the American College of Allergy and Immunology, Los Angeles,CA, Nobember 1988.

26. "Multiple-Dose Pharmacokinetic Evaluation of a Once-Daily Theophylline Tablet Doses to Pediatric Asthmatics", Third Eastern Allergy Conference, Bal Harbour, FL Apr 1990.

27. "Effect of Tablet Halving on the Pharmacokinetics of Theophylline from Uni-Dur", ACCP Annual Meeting, Kansas City, MO, Aug 1990.

28. "Bioavailability of Eight Trichlormethiazide Tablet Formulations," AAPS Annual Meeting, Atlanta, GA, Nov 1989.

29. "Gastric pH and Absorption of Cr-Theophylline Products in Man", AAPS Annual Meeting, Atlanta, GA, Nov 1989.

30. "Bioequivalence of Methylphenidate Tablets", AAPS Annual Meeting, Las Vegas, NV, Nov 1990.

31. "Influence of Gastric pH on the Absorption of Diazepam", AAPS Annual Meeting, Las Vegas, NV, Nov 1990.

32. "Bioequivalence of Theophylline Immediate Release Tablets" AAPS Annual Meeting, Las Vegas, NV, Nov 1990.

33. "Multiple Dose Pharmacokinetic Evaluation of a Once Daily Theophylline Tablet Dosed to Pediatric Asthmatics", 3rdEastern Allergy Conference, Bal Harbour, FL 1990.

34. "Pharmacokinetics of Uni-Dur, a Once Daily Theophylline" Annual Conference of the European Respiratory Society, Brussels, Belgium Sept 1991.

35. "Formulation Dependent Steady State Chronopharmacokinetics of Theophylline", AAPS Annual Meeting, Washington, DC, Nov 1991.

36. "The Bioavailability of Multi-Source Amitriptyline Formulations", AAPS Annual Meeting, Washington, DC, Nov 1991.

37. "Effect of Reformulation on the Bioavailability of 50 mg Primidone Tablets", AAPS Annual Meeting, SanAntoino, TX Nov 1992.

Abstracts: (Cont.)

38. "The effect of Food on the Bioavailability of Doxycycline Hyclate Capsules and Tablets," Annual Meeting, Orlando, FL Nov 1993.

39. "The Effect of Reformulation on the bioequivalence of 250 mg Primidone Tablets," AAPS Annual Meeting, Orlando, FL Nov 1993.

40. "Bioequivalence (BE) of Multi_source Carbamazepine (CBZ) Tablets," AAPS Annual Meeting, San Diego, CA Nov 1994.

41. "Correlation Between In Vitro Dissolution and In Vivo Oral Bioavailability of Piroxicam (PR) Capsules," AAPS Annual Meeting, San Diego, CA Nov 1994.

42. "Pavlovian Food Effect on Enterohepatic Recirculation Monitored by Drug Plasma Concentration: Piroxicam Example," AAPS Annual Meeting, San Diego, CA Nov 1994.

43. "Use of the Heidelberg Capsule to Evaluate the Effects of Food on the Bioavailability of an Enteric-Coated Tablet with Rapid Abosrption and Elimination," AAPS Annual Meeting, San Diego, CA Nov 1994.

44. "Bioequivalence(BE) of Different Lots of Dilantin," AAPS Annual Meeting, Seattle, WA Oct 1996.

46. "Bioequivalence(BE) of Marketed Multisource Desipramine (DE) Products and the Effects of Gender Differences," AAPS Annual Meeting, Seattle, WA Oct 1996.

47. "Carbamazepine Level-A In Vitro-In Vivo (VV) Correlation: A scaled Convolution Based Predictive Approach," AAPS Annual Meeting, Seattle, WA Oct 1996.

48. "The Effects of Cross Linking in Gelatin Capsules on the Bioequivalence of Acetaminophen", AAPS Annual Meeting, Boston, MA Nov 1997.

49. " The Effect of Hormonal Fluctuation During the Menstrual Cycle on the Pharmacokinetics of Tobramycin", AAPS Southern Regional Discussion jJGroup, Oxford, MS May 1998.

50. " The Pharmacokinetics of Chlorpheniramine, Phenytoin, Nifepidine and Glipizide in an Individual Homozygous for the LEU359 Allele of CYP 2C90", AAPS Southern Regional Discussion jJGroup, Oxford, MS May 1998.

Invited Presentations:

1. "Digoxin Intoxication: Case Study", Grand Rounds UTCHS, Memphis, Tennessee, Aug, 1976.

2. "Pharmacokinetic Considerations in Aminoglycoside Therapy", Arkansas Society of Hospital Pharmacists Fall Seminar, Little Rock, Arkansas, Sept, 1976.

3. "Basic Concepts in Clinical Pharmacokinetics", Seattle Area Society of Hospital Pharmacists Annual Seminar, Seattle, Washington, March, 1977.

4. "Bioavailability Aspects of Drug Therapy", Annual St. Thomas Moore-Roche Therapeutic Symposium, Nashville, Tennessee, Aug, 1977.

5. "Basic Pharmacokinetics", UTCHS College of Medicine Continuing Education Program, Memphis, Tennessee, March, 1978.

6. "The Digitalis Glycosides" and "The Aminoglycosides Antibiotics", Radioassay Applications in Pharmacology and Hematology, Veterans Administration Hospital, St. Louis, Missouri, Apr, 1978.

7. "Pharmacokinetic Aspects of Toxicology", Clinical Toxicology and Pharmacology, VA Hospital, Memphis, Tennessee, June, 1979.

8. "Drug Dosing Concepts", Clinical Toxicology and Pharmacology, VA Hospital, Memphis, Tennessee, August 27, 1980.

9. "A Diurnal Pharmacokinetic Model for Multiple Dose Theophylline", College of Pharmacy, University of Utah, Salt Lake City, Utah, Apr, 1983.

10. "Chronopharmacokinetics", College of Pharmacy, Medica College of Virginia, Richmond, Virginia, May, 1983.

11. "Power Analysis in Bioavailability Studies", Glaxo Laboratories, Research Triangle Park, N.C., Dec, 1983.

12. "Practical Aspects of Therapeutic Drug Monitoring", Winchester County Society of Hospital Pharmacists, Valhalla, N.Y., May, 1984.

13. "Administration of Theo-Dur Once-A-Day vs. Twice-A-Day" Sustained Release Theophylline and Nocturnal Asthma Workshop, Burgenstock, Switzerland, July, 1984.

14. "Interpretation of Bioavailability Data for the Practitioner", ASHP Mid-Year Clinical, New Orleans, LA, Dec, 1985.

15. "Controversies in Sustained-Release Theophylline", HamiltonCo. Pharmaceutical Society, Chattanooga, TN, March, 1986.

16. "Absorption of pH Dependent SR Theophylline in Patients with Normal and Decreased Gastric Acid Production," Schering Corporation, Miami, FL, June, 1987.

17. "PharMACokinetix: A Pharmacokinetic Simulation Tool, 18thAnnual Meeting of EDUCOM, Los Angles, CA, November, 1987.

Invited Presentations(Cont.):

18. "Bar Code Reading for In-process Quality Control of Clinical Data," 24th Annual Meeting of the Drug Information Association, Toronto, Canada, July 1988.

19. "Pharmacokinetics of a New Once-a-Day Theophylline", 45thAnnual Congress of the College of Allergy and Immunology. LosAngles CA, Nov, 1988.

20. "Optical Scanning for Clinical Data Capture and Tracking" DIA Workshop on Clinical Data Management, Philadelphia, PA, Apr, 1989.

21. "Pharmacokinetics of 'Once-A-Day' Theophylline, Cancun Conference, Cancun, Mexico, May, 1989.

22. "Dosage Regimens for SR Theophylline", 2nd International Colloquium on Progress in Pulmonary Medicine, Deauville, France, June, 1989.

23. "Pharmacokinetics of a New Onec-a-Day Theophylline, Medical Education Conference, Dallas, Tx, Sept, 1989.

24. "Pharmaceutical Aspects of Theophylline Dosage Forms", Medical Education Conference, Houston, TX, Nov, 1989.

25. "Dosing Considerations of Once-a-Day Theophylline, MedicalEducation Conference, New York, NY, Dec, 1989.

26. "Bathrooms and Bioinequivalence:Problems with Carbamazepine, Schering Research, Miami, FL, March, 1989.

27. "Carbamazepine Bioavailability", Ciba-Giegy, Morristown, NJ, Oct 1990.

28. "Sustained-Release Theophylline", Carnrick Pharmaceuticals, Dallas TX, Apr, 1992.

29. "Ethics and the Industrial/Academic Relationship", Ethics in Medicine Seminar Series, Memphis, TN, June, 1993.

30. "How We Got the Bucks- Pharmaceutical Studies," A UTRC Hertel Event, Memphis, TN, May, 1994 and April, 1995.

31. "Pharmacokinetic Workshop Using Stella Simulation Software," Faulding Pharmaceuticals, Adelaide, Australia, December 1994.

32. "Optomization of Drug Formulations Using In Vitro/In Vivo Modeling with STELLA", Kemic Course in the Pharmaceutical Scineces Philidelphia PA, May 1997

Research Grant Awards:

Co-Investigator "Bioavailability Evaluation Program"	U.S. Food and Drug Administration	June 1974- June 1975	$ 44,850
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1974- June 1975	$ 130,000
Co-Investigator "Bioavailability Evaluation Program"	U.S. Food and Drug Administration	July 1975 June 1976	$ 58,000
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1975 June 1976	$ 130,000
Co-Investigator "Bioavailability Evaluation Program"	U.S. Food and Drug Administration	July 1976 June 1977	$ 53,300
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1976- June 1977	$ 130,000
Principal Investigator "Pharmacokinetics Use in Developing Theophylline Dosage Regimens"	Cooper Laboratories	Sept.1976	$ 2,500
Co-Investigator "Bioavailability Studies"	Bell Pharmacal	Feb. 1977	$ 8,000
Co-Investigator "Bioavailability Studies"	Cooper Laboratories	Mar. 1977	$ 16,000
Co-Investigator "Bioavailability Studies"	Cord Laboratories	May 1977	$ 16,000
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1977- June 1978	$ 130,000
Co-Investigator "Bioavailabiliyv Studies"	Cooper Laboratories	July 1978	$ 16,200
Co-Investigator "Bioavailability Evaluation Program"	U.S. Food and Drug Administration	Sept.1977- Aug. 1980	$ 271,300
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1978- June 1979	$ 130,000

Research Grant Awards (Continued):

Co-Investigator "Clinical Pharma-cokinetics of Cancer Drugs"	National Cancer Institute - NIH	Sept.1978-Aug. 1979	$ 27,500
Co-Investigator "Bioavailability Studies"	Cooper Laboratories	Oct. 1978	$ 17,000
Principal Investigator "Sustained-Release Drug Bioavailability"	Key Pharmaceuticals	Mar. 1979	$ 7,000
Co-Investigator "Bioavailability Studies"	Marion Laboratories	Apr.1979	$ 19,200
Co-Investigator "Bioavailability Studies"	Cooper Laboratories	June 1979	$ 11,600
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1979-June 1980	$ 130,000
Co-Investigator "Bioavailability Studies"	Pharmadyne Corp.	Aug. 1979	$ 14,800
Co-Investigator "Bioavailability Studies"	Meyer-Glaxo Labs.	Dec. 1979	$ 17,000
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Mar. 1980	$ 25,500
Co-Investigator "Bioavailability Studies"	Meyer-Glaxo Labs.	Apr. 1980	$ 24,500
Co-Investigator "Bioavailability Studies"	Berlex Laboratories	July 1980	$ 13,000
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1980-June 1981	$ 130,000
Co-Investigator "Bioavailability Evaluation Program"	U.S. Food and Drug Administration	Aug. 1980-Dec. 1980	$ 35,000
Co-Investigator "Bioavailability Studies"	Berlex Laboratories	Oct. 1980	$ 9,800
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Jan. 1981	$ 29,600
Co-Investigator "Bioavailability Studies"	Glaxo Laboratories	Jan. 1981	$ 41,000

Research Grant Awards (Continued):

Co-Investigator "Bioavailability Studies"	Cord Laboratories	Jan. 1981	$ 42,500
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Feb. 1981	$ 22,000
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	May 1981	$ 5,000
Principal Investigator "Aspirin Pharmacokinetics in Arthritis"	Bristol-Myers Labs	July 1981	$ 1,400
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	July 1981	$ 8,000
Co-Principal Investigator "Quinidine Bioavailability Studies"	Key Pharmaceuticals	Sept.1981	$ 16,000
Co-Investigator "Metronidazole Bioavailability Studies"	Cord Laboratories	Jan. 1982	$ 26,000
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	Feb. 1982	$ 8,800
Co-Investigator "Ceftazidime Pharmacokinetics in Renal Patients"	Glaxo, Inc.	Feb. 1982	$ 34,300
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	July 1982	$ 25,000
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee	July 1982-June 1983	$ 180,000
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Aug. 1982	$ 11,800
Co-Investigator "Ceftazidime Pharmacokinetics During CAPD"	Glaxo, Inc.	Aug. 1982	$ 15,000
Co-Investigator "Bioavailability Studies"	Pennwalt Corporation	Sept 1982	$ 28,026

Research Grant Awards (Continued):

Co-Investigator "Naltrexone Pharmacokinetics"	DuPont Corporation	Nov. 1982	$ 39,240
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	Nov. 1982	$ 9,000
Co-Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Nov. 1982	$ 14,000
Co-Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Dec. 1982	$ 18,000
Principal Investigator "Multiple Dose Drug Studies"	Key Pharmaceuticals	Feb. 1983	$ 36,000
Co-Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Feb. 1983	$ 18,000
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	Apr. 1983	$ 22,900
Co-Principal Investigator "Transdermal Dosing"	Key Pharmaceuticals	July 1983	$ 6,750
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1983-June 1984	$ 180,000
Co-Principal Investigator "Food Effect on Cefuroxime"	Glaxo, Inc.	Nov. 1983	$ 59,400
Co-Principal Investigator "Aspirin Multiple Dosing"	International Drug Registration	Nov. 1983	$ 65,869
Co-Investigator "Bioavailability Studies"	Danbury Pharmacal	Dec. 1983	$ 31,500
Co-Principal Investigator "Bioavailability Studies"	Purdue Frederick Co.	Dec. 1983	$ 28,800
Principal Investigator "Sustained-Release Theophylline"	Key Pharmaceuticals	Jan. 1984	$ 51,000
Co-Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Jan. 1984	$ 11,400
Co-Investigator "Cefoperazone/Sulbactam"	Pfizer Pharmaceuticals	Feb. 1984	$ 43,000

Research Grant Awards (Continued):

Principal Investigator "Bioavailability Studies"	Pennwalt Corporation	Mar. 1984	$ 5,000
Co-Investigator "Bioavailability Studies"	International Drug Registration	Mar. 1984	$ 31,088
Co-Investigator "Theophylline Bioavailability Studies"	Purdue Frederick Co.	Mar. 1984	$ 36,475
Co-Principal Investigator "Bioavailability Studies"	Sidmak Laboratory	Apr. 1984	$ 24,767
Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Apr. 1984	$ 29,330
Principal Investigator "Bioavailability Studies"	Danbury Pharmacal	May 1984	$ 23,599
Co-Investigator "Drug Absorption in Achlorhydric Patients"	U.S. Food and Drug Administration	June 1984-June 1987	$ 558,000
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1984-June 1985	$ 180,000
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	July 1984	$ 23,526
Co-Principal Investigator "Plasma Binding and Excretion"	Cord Laboratories	July 1984	$ 89,000
Co-Investigator "Absorption Studies"	Duramed Pharm.	Aug. 1984	$ 16,200
Principal Investigator "Theophylline Bioavailability Studies"	Key Pharmaceuticals	Aug. 1984	$ 21,266
Principal Investigator "Absorption Studies"	Key Pharmaceuticals	Sept. 1984	$ 22,000
Co-Investigator "Bioavailability Studies"	Pennwalt Corporation	Oct. 1984	$ 36,500
Co-Investigator "Bioavailability Studies"	International Drug Registration	Nov. 1984	$ 25,000
Principal Investigator "Temocillin Pharmacokinetics"	Beecham Laboratories	Mar. 1985	$ 46,300

Research Grant Awards (Continued):

Principal Investigator "Bioavailability Studies"	Key Pharmaceuticals	Mar. 1985	$ 11,000
Principal Investigator "Steady-State Bioavailability Studies"	Key Pharmaceuticals	Apr. 1985	$ 17,863
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1985 June 1986	$ 142,015
Principal Investigator "Theophylline Studies"	Key Pharmaceuticals	Aug. 1985	$ 20,900
Principal Investigator "Quinidine Studies"	Key Pharmaceuticals	Sept.1985	$ 25,600
Co-Investigator Propranolol/Hydrochlorothiazide"	Quincy Laboratories	Sept.1985	$ 67,600
Co-Investigator "Dipyridamole Bioavailability"	Cord Laboratories	Oct. 1985	$ 73,000
Principal Investigator "Cefuroxime Food Studies"	Glaxo, Inc.	Dec. 1985	$ 19,700
Co-Investigator "Dipyridamole Bioavailability"	Colmed Laboratories	Jan. 1986	$ 32,000
Co-Principal Investigator "Single and Multiple Dose Theophylline Studies"	Cord Laboratories	Apr. 1986	$ 86,540
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1986- June 1987	$ 142,015
Co-Investigator "Griseofulvin Absorption"	Sidmak Laboratories	May 1986	$ 67,300
Principal Investigator "Ranitidine Studies"	Glaxo Laboratories	May 1986	$ 18,716
Principal Investigator "Gastric pH Effect on Theophylline Absorption"	Key Pharmaceuticals	July 1986	$ 21,421
Principal Investigator "Single Daily Dosing for Theophylline"	Schering Corporation	Aug. 1986	$ 16,853

Research Grant Awards (Continued):

Co-Investigator "Bioavailability Study"	Ganes Chemical Co., New York, NY	Jan. 1987	$ 23,500
Co-Investigator "Theophylline Absorption"	Sidmak Laboratories	Jan. 1987	$ 56,314
Principal Investigator "Theophylline Kinetics"	Glaxo, Inc.	Jan. 1987	$ 22,275
Principal Investigator Pilot Study on Food Effect on Theophylline Absorption"	Schering Corporation	Jan. 1987	$ 14,786
Co-Investigator "Pharmacokinetic Study"	Beecham Laboratories	Feb. 1987	$ 70,000
Co-Investigator "Dinoseb Pharmacokinetics"	Dinoseb Task Force II	Mar. 1987	$ 62,500
Principal Investigator "Theophylline Studies"	Schering Corporation	Mar. 1987	$ 63,120
Co-Investigator "Dipyridamole Study"	Vitarine	Mar. 1987	$ 32,000
Co-Investigator "Drug Quality Assurance Program"	State of Tennessee Department of Public Health	July 1987 June 1988	$ 142,015
Co-Investigator "Bioavailability Studies"	Sidmak Laboratories	May 1987	$ 25,200
Co-Investigator "Steady-State SR Formulations"	Sidmak Laboratories	July 1987	$ 97,800
Co-Investigator "Bioreplication Studies"	Siegfried AG	Aug. 1987	$ 57,600
Principal Investigator "Theophylline Kinetics at SS"	Schering Corporation	Aug. 1987	$ 30,000
Co-Investigator "Bioavailability Evaluation"	US Food and Drug Administration	Sept.1987- Sept.1990	$ 487,725
Co-Investigator "Bioavailability Studies"	Sidmak Laboratories	Oct. 1987	$ 64,500
Principal Investigator "SR Theophylline Study"	Schering Corporation	Nov. 1987	$ 43,800

Research Grant Awards (Continued):

Co-Investigator "Aspirin Studies"	IDR	Jan. 1988	$ 34,000
Principal Investigator "Re-encapsulated Theophylline"	Glaxo, Inc.	Jan. 1988	$ 28,746
Principal Investigator "Food Effect SR Theophylline"	Schering Corporation	Feb. 1988	$ 63,029
Co-Investigator "Steady-State Study"	Sidmak Laboratories	Mar. 1988	$ 44,200
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1988-June 1989	$ 142,015
Principal Investigator "Theophylline Kinetics"	Schering Corporation	Sept.1988	$ 17,820
Co-Investigator "New Assay Methods"	Sidmak Laboratories	Oct. 1988	$ 30,000
Principal Investigator "Theophylline Bioavailability"	Schering Corporation	Nov. 1988	$ 23,640
Co-Investigator "Griseofulvin Bioavailability"	Sidmak Laboratories	Nov. 1988	$ 88,000
Principal Investigator "Theophylline Bioavailability"	Schering Corporation	Dec. 1988	$ 27,930
Co-Investigator "Diazepam Studies"	Vitarine Laboratories	Mar. 1989	$ 34,000
PrincipalInvestigator "Pediatric Theophylline"	ScheringCorporation	April 1989	$ 8,420
Principal Investigator "Aspirin Effect on Niacin Induced Flushing"	Kos Pharmaceuticals	Apr 1989	$ 3,280
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1989-June 1990	$ 106,897
Principal Investigator "Antacids and Theophylline"	Schering Corporation	Nov. 1989	$ 38,960
Principal Investigator "Ped S-R Theo Kinetics"	Schering Corporation	Dec. 1989	$ 14,850

Research Grant Awards (Continued):

Principal Investigator "Theophylline Kinetics"	Schering Corporation	Dec. 1989	$ 15,120
Principal Investigator "Steady-State Theophylline"	Schering Corporation	Dec. 1989	$ 16,200
Principal Investigator "Steady-State Theophylline"	Schering Corporation	Dec. 1989	$ 16,200
"Principal Investigator "New Dosage Forms"	Kos Pharmaceuticals	Apr. 1990	$ 13,220
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1990-June 1991	$ 106,897
Principal Investigator "Food Effect on Sprinkle"	Schering Corporation	July 1990	$ 53,840
Principal Investigator "Sprinkle/Intact Dosages	Schering Corporation	Aug. 1990	$ 18,389
Principal Investigator "Food Effect on Absorption"	Kos Pharmaceuticals	Sep. 1990	$ 31,384
Principal Investigator "Pilot Effect of Food"	Kos Pharmaceuticals	Dec. 1990	$ 14,400
Principal Investigator "Flux Studies"	Venture Pharma.	Dec. 1990	$ 6,000
Principal Investigator "Single Dose Theophylline"	Schering Corporation	Dec. 1990	$ 58,638
Principal Investigator "Steady-State Once-a-Day Theophylline Sprinkle"	Schering Corporation	Dec. 1990	$ 20,375
Co-Investigator "Bioavailability Studies"	Vitarine	Jan. 1991	$ 31,000
Principal Investigator "Uni-Dur Absorption"	Schering Corporation	Jan. 1991	$ 47,082
Co-Principal Investigator "Clonazepam pH Dependent Absorption"	Hoffman LaRoche	Feb. 1991	$ 69,000
Co-Prinicpal Investigator "Urinary Excretion of NFT	Vitarine	Feb. 1991	$ 16,300

Research Grant Awards (Continued):

Prinicpal Investigator "Uni-Dur Analytical"	Schering Corporation	Aug. 1991	$ 38,400
Co-Principal Investigator "Cyclobenzaprine Absorption"	MD Pharmaceuticals	July 1991	$ 79,488
Co-Investigator "DrugQuality Assurance Program"	State of Tennessee Department of Public Health	July 1991- June 1992	$ 106,695
Co-Principal Investigator "Generic Drug Studies"	U.S. Food and Drug Administration	July 1991- June 1994	$ 584,575
Principal Investigator "Transdermal Drug Delivery"	Kos Pharmaceuticals	Oct. 1991	$ 22,507
Principal Investigator "In Vitro Flux Studies"	Sano Corporation	Oct. 1991	$ 12,000
Principal Investigtator "Sport Gel in Women"	Sano Corporation	Nov. 1991	$ 21,900
Principal Investigator "In Vivo Flux Study"	Sano Corporation	Apr. 1992	$ 12,072
Principal Investigator "Sport Gen in Women II"	Whitby Research	Apr. 1992	$ 21,900
Principal Investigator "SR Theophylline Kinetics"	Ciba-Geigy	Aug. 1992	$ 31,759
Co-principal Investigator "Gastric Emptying and Enteric Coated Tablets"	Schering-Plough	Jan. 1993	$ 57,250
Co-principal Investigator "Antihistamine Pharmacodynamics"	Kos Pharmaceuticals	Mar. 1993	$ 83,000
Principal Investigator "Absorption of SR Theophylline"	Eon Labs	Apr. 1993	$ 36,687
Co-principal Investigator "Multiple Bioavailability Studies"	Sano Corporation	Apr. 1993	$ 170,000
Principal Investigator "Transdermal Absorption of Drugs"	Timerx Technologies	July 1993	$ 28,692
Principal Investigator "SR Drug Release Properties in Humans"		Sept 1993	$ 48,234

Research Grant Awards (Continued):

Co-principal Investigator "Effect of Formulation on Piroxicam Absorption"	Univ. of Maryland Subcontract FDA	July 1993	$ 115,959
Co-Principal Investigator "Generic Drug Studies"	U.S. Food and Drug Administration	July 1994-Jan 1995	$ 110,000
Principal Investigator "SR Albuterol Food Effects	Timerx Technologies	Sept 1994	$ 27,970
Principal Investigator "Effect of Food on Pseudoephedrine Absorption in Humans"	Timerx Technologies	Nov 1994	$ 29,193
Co-Principal Investigator "Generic Drug Studies"	U.S. Food and Drug Administration	Jan 1995-Jan 1998	$ 689,000
Principal Investigator "Transdermal Absorption of Drugs in Humans"	Sano Corporation	Jan 1995	$ 29,156
Principal Investigator "Albuterol Absorption"	Timerx Technologies	March 1995	$ 21,956
Principal Investigator "Effect of Food on Nifedipine"	Timerx Technologies	April 1995	$ 30,736
Principal Investigator "SR Nifedipine Absorpiton	Timerx Technologies	April 1995	$ 30,736
Principal Investigator "SR Nifedipine Absorpiton	Timerx Technologies	May 1995	$ 34,803
Principal Investigator "Transdermal Absorption of Drugs in Humans"	Sano Corporation	Jan 1996	$ 49,478
Principal Investigator "SR Drug Absorption"	Timerx Technologies	August 1995	$ 44,913
Principal Investigator "Effect of Food on Nifedipine"	Timerx Technologies	October 1995	$ 39,714
Principal Investigator "SR Nifedipine Absorpiton"	Timerx Technologies	October 1995	$ 44,913
Principal Investigator "SR Nifedipine Absorpiton"	Timerx Technologies	January 1996	$ 68,906
Principal Investigator "Effect of Food on Nifedipine"	Timerx Technologies	January 1996	$ 39,768
Co-Investigator "Bioavailability of Dosage Forms"	Daniels Pharmaceuticals	October 1995	$ 57,231

Co-Investigator "IV vs Oral Dosage Forms"	Dusa Pharmaceuticals	January 1996	$ 54,340
Principal Investigator "Bioavailability of Dosage Forms"	Timerx Technologies	July 1996	$ 47,583
Principal Investigator "Bioavailability of Dosage Forms"	Timerx Technologies	October 1996	$ 39,493
Principal Investigator "Bioavailability of Dosage Forms"	Timerx Technologies	November 1996	$ 114,678
Co- Investigator "Bioavailability (Pilot Study)"	Psoralen, Inc.	December 1996	$ 16,288
Co- Investigator "Bioavailability and Food"	Psoralen, Inc.	December 1996	$ 59,514
Principal Investigator "Bioavailability of Dosage Forms"	Timerx Technologies	October 1997	$ 118,541
Principal Investigator "Bioavailability of Dosage Forms"	Penwest Pharmaceutical	January 1998	$ 174,645
Principal Investigator "Drug Flux Studies"	Sano Corporation	Jan 1997	$ 26,290
Total Funding			$10,510,835

PDR

51

EDITION

1997

PHYSICIANS' DESK REFERENCE®

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EXHIBIT #2

o oe administered rectally. *For Analgesia*—Usual Adult
: 10 to 30 mg every 4 hours or as directed by physician:
ge is a patient dependent variable, and increased dosage
be required for adequate analgesia. For control of
ic, agonizing pain in patients with certain terminal
es, this drug should be administered on a regularly
duled basis, every 4 hours, at the lowest dosage level
will achieve adequate analgesia. Note: Medication may
ress respiration in the elderly, the very ill, and those
nts with respiratory problems, therefore lower doses
be required.

PHINE DOSAGE REDUCTION

g the first two to three days of effective pain relief, the
nt may sleep for many hours. This can be misinter-
d as the effect of excessive analgesic dosing rather than
rst sign of relief in a pain exhausted patient. The dose,
fore, should be maintained for at least three days before
tion, if respiratory activity and other vital signs are
ate. Following successful relief of severe pain, periodic
pts to reduce the narcotic dose should be made.
er doses or complete discontinuation of the narcotic
esic may become feasible due to a physiologic change or
nproved mental state of the patient.

SUPPLIED

Suppositories are individually sealed in color-coded
pers to aid in identification. 5 mg suppositories (white
per/blue type), NDC 0245-0160-12, 12 per carton. 10 mg
sitories (white wrapper/green type), NDC 0245-0161-
per carton. 20 mg suppositories (white wrapper/red
NDC 0245-0162-12, 12 per carton. 30 mg suppositories
wrapper/gold type), NDC 0245-0163-12, 12 per carton.
ORDER FORM REQUIRED—
n: Federal law prohibits dispensing without prescrip-

:® ℞

sium Iodide Oral Solution, USP
ated) 1 g/ml

RIPTION

(potassium iodide oral solution, USP) is a saturated
n of potassium iodide containing 1 g of potassium
per ml.

ICAL PHARMACOLOGY

ium iodide is thought to act as an expectorant by in-
g respiratory tract secretions and thereby decreasing
cosity of mucus.

ATIONS AND USAGE

e as an expectorant in the symptomatic treatment of
c pulmonary diseases where tenacious mucus compli-
he problem, including bronchial asthma, bronchitis
lmonary emphysema.

RAINDICATIONS

indicated in patients with a known sensitivity to io-

INGS

um iodide can cause fetal harm, abnormal thyroid
n, and goiter when administered to a pregnant
. Because of the possible development of fetal goiter,
rug is used during pregnancy or if the patient becomes
nt during therapy, apprise the patient of the potential

AUTIONS

l: In some patients, prolonged use of iodides can
hypothyroidism. Iodides should be used with caution
nts having Addison's disease, cardiac disease, hyper-
ism, myotonia congenita, tuberculosis, acute bronchi-
renal function impairment.
nteractions: Concurrent use with lithium and other
roid drugs may potentiate the hypothyroid and goi-
c effects of these medications. Concurrent use with
um-containing medications, potassium-sparing di-
and angiotensin-converting enzyme inhibitors (ACE
rs) may result in hyperkalemia and cardiac arrhyth-
cardiac arrest.
aboratory Test Interactions: Thyroid function tests
altered by iodide.
ncy: Category D—see "Warnings" section.
g Mothers: Potassium iodide is excreted in breast
se by nursing mothers may cause skin rash and thy-
pression in the infant.
c Use: Safety and effectiveness in children have
n established.

SE REACTIONS

t frequent adverse reactions to potassium iodide are
upset, diarrhea, nausea, vomiting, stomach pain,
h, and salivary gland swelling or tenderness. Less
adverse reactions include gastrointestinal bleeding,
n, irregular heartbeat, numbness, tingling, pain or
weakness in hands or feet, unusual tiredness, weakness or heaviness of legs, fever, and swelling of neck or throat. Thyroid adenoma, goiter, and myxedema are possible side effects.

Iodism or chronic iodine poisoning may occur during prolonged treatment or with the use of high doses. The symptoms of iodism include burning of mouth or throat, severe headache, metallic taste, soreness of teeth and gums, symptoms of head cold, irritation of the eyes with swelling of the eyelids, unusual increase in salivation, acneform skin lesions in the seborrheic areas, and rarely, severe skin eruptions. If symptoms of iodism appear, the drug should be withdrawn and the patient given appropriate supportive therapy.

Hypersensitivity to iodides may occur and may be manifested by angioedema, cutaneous and mucosal hemorrhage, and signs and symptoms resembling serum sickness, such as fever, arthralgia, lymph node enlargement, and eosinophilia.

OVERDOSAGE

Acute toxicity from potassium iodide is relatively rare. An occasional individual may show marked sensitivity and the onset of acute poisoning can occur immediately or hours after administration. Angioedema, laryngeal edema and cutaneous hemorrhages may occur.

Iodism or chronic iodine poisoning may occur during prolonged treatment or with the use of high doses. Symptoms of iodism typically disappear soon after discontinuation of the drug. Abundant fluid and salt intake aids in iodide elimination.

DOSAGE AND ADMINISTRATION

Adults—0.3 ml (300 mg) or 0.6 ml (600 mg) diluted in one glassful of water, fruit juice or milk 3 to 4 times daily. To minimize gastric irritation, take with food or milk.

The medication should be used no longer than is necessary to produce the desired effect.

HOW SUPPLIED

SSKI® (potassium iodide oral solution, USP) is supplied in 1 fluid ounce (30 ml) bottles (NDC 0245-0003-31) with a calibrated dropper marked to deliver 0.3 ml (300 mg) and 0.6 ml (600 mg); and 8 fluid ounce (237 ml) bottles (NDC 0245-0003-08). Inactive ingredient: Sodium thiosulfate as a preservative.

Caution: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 59°–86° F (15°–30°C). Keep tightly closed and protect from light.

Dispense in tight, light resistant containers with child resistant closures.

Notice: When exposed to cold temperatures, crystallization may occur, but on warming and shaking, the crystals will redissolve. If the solution turns brownish yellow in color, it should be discarded.

SALSITAB® ℞
[sal' si "tab]
Salsalate
Tablets

DESCRIPTION

Salsitab® (salsalate) is a nonsteroidal anti-inflammatory agent for oral administration.

Each round, blue, film coated Salsitab® Tablet contains 500 mg salsalate. Each capsule-shaped, blue, scored, film coated Salsitab® Tablet contains 750 mg salsalate.

HOW SUPPLIED

500 mg tablets in bottles of 100 (NDC 0245-0153-11)
500 mg tablets in bottles of 500 (NDC 0245-0153-15)
500 mg tablets in cartons of 100 unit dose (NDC 0245-0153-01)
750 mg tablets in bottles of 100 (NDC 0245-0154-11)
750 mg tablets in bottles of 500 (NDC 0245-0154-15)
750 mg tablets in cartons of 100 unit dose (NDC 0245-0154-01)

SLO-NIACIN® Tablets OTC
(polygel® controlled-release niacin)
Dietary Supplement

DESCRIPTION

Slo-Niacin® Tablets are manufactured utilizing a unique, patented polygel® controlled-release delivery system. This exclusive technology assures the gradual and measured release of niacin (nicotinic acid) and is designed to reduce the incidence of flushing and itching commonly associated with niacin use. Slo-Niacin® Tablets are available in 250 mg, 500 mg, and 750 mg strengths.

SUGGESTED USE

Slo-Niacin® is a member of the vitamin B-complex group (nicotinic acid, vitamin B_3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

DIRECTIONS

250 mg: Adults—One Slo-Niacin® Tablet morning or evening, or as directed by a physician.
500 mg: Adults—One Slo-Niacin® Tablet morning or evening, or as directed by a physician.
750 mg: Adults—One-half Slo-Niacin® Tablet morning or evening, or as directed by a physician.
Before using more than 500 mg daily, consult a physician.
Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.
Store at room temperature, 59°–86°F.
Keep tightly closed.

CAUTION

Niacin may cause temporary flushing, itching and tingling, feelings of warmth and headache, particularly when beginning, increasing amount or changing brand of niacin. These effects seldom require discontinuing niacin use. Skin rash, upset stomach, and low blood pressure when standing are less common symptoms; if they persist, contact a physician.

WARNINGS

Slo-Niacin® Tablets should not be used by persons with a known sensitivity or allergy to niacin. Persons with heart disease, particularly those who have recurrent chest pain (angina) or who recently suffered a heart attack, should take niacin only under the supervision of a physician. Persons taking high blood pressure or cholesterol-lowering drugs should contact a physician before taking niacin because of possible interactions. Do not take niacin unless recommended by and taken under the supervision of a physician if you have any of the following conditions; gallbladder disease, gout, arterial bleeding, glaucoma, diabetes, impaired liver function, peptic ulcer, pregnancy or lactating women. Increased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500 mg or more of niacin.

Discontinue use and consult a physician immediately if any of the following symptoms occur: persistent flu-like symptoms (nausea, vomiting, a general "not well" feeling); loss of appetite; a decrease in urine output associated with dark-colored urine; muscle discomfort such as tender, swollen muscles or muscle weakness; irregular heartbeat; or cloudy or blurry vision.

Keep out of the reach of children.

INGREDIENTS

250 mg niacin (nicotinic acid), supplying 1,250% of the Reference Daily Intake (RDI) for niacin.
500 mg niacin (nicotinic acid), supplying 2,500% of the Reference Daily Intake (RDI) for niacin.
750 mg niacin (nicotinic acid), supplying 3,750% of the Reference Daily Intake (RDI) for niacin.
Each tablet also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red # 40.

HOW SUPPLIED

250 mg tablets in bottles of 100: List No. 0245-0062-11
500 mg tablets in bottles of 100: List No. 0245-0063-11
750 mg tablets in bottles of 100: List No. 0245-0064-11
U.S. Patent No. 5,126,145 and other patents pending.

Shown in Product Identification Guide, page 339

Vitaline Corporation
385 WILLIAMSON WAY
ASHLAND, OR 97520

Direct Inquiries to:
Jed D. Meese, Technical Director
(541) 482-9231
FAX: (541) 482-9112

L-CARNITINE USP OTC
250mg Tablets, 500mg Scored Caplets and 500mg Chewable Wafers
Renal Patient L-Carnitine
Dietary Supplement

DESCRIPTION

Carnitine is a naturally occurring substance, and is essential for fatty acid oxidation and energy production. Without it, long-chain fatty acids cannot cross from cellular cytoplasm

Continued on next page

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UPSHER-SMITH

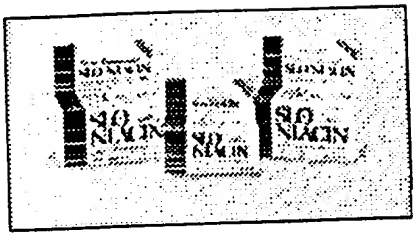
Excellence Through Innovation

Slo-Niacin®

polygel® controlled-release niacin

DIETARY SUPPLEMENT

When tolerability is a concern



View Pharmacy Flyer

What You Should Know About Your Cholesterol & Niacin

DESCRIPTION

Slo-Niacin® Tablets are manufactured utilizing a unique, patented polygel® controlled-release delivery system. This exclusive technology assures the gradual and measured release of niacin (nicotinic acid) and is designed to reduce the incidence of flushing and itching commonly associated with niacin use. Slo-Niacin® Tablets are available in 250 mg, 500 mg, and 750 mg strengths.

SUGGESTED USE

Slo-Niacin® is a member of the vitamin B-complex group (nicotinic acid, vitamin B-3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

DIRECTIONS

250 mg: Adults -- one Slo-Niacin® Tablet morning or evening, or as directed by a physician.

500 mg: Adults -- one Slo-Niacin® Tablet morning or evening, or as directed by a physician.

750 mg: Adults -- one-half Slo-Niacin® Tablet morning or evening, or as directed by a physician.

EXHIBIT #3

Before using more than 500 mg daily, consult a physician.

Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.

Store at controlled room temperature, 15-30° C(59-86° F)

CAUTION

Niacin may cause temporary flushing, itching and tingling, feelings of warmth and headache, particularly when beginning, increasing amount or changing brand of niacin. These effects seldom require discontinuing niacin use. Skin rash, upset stomach, and low blood pressure when standing are less common symptoms; if they persist, contact a physician.

WARNINGS

Slo-Niacin® Tablets should not be used by persons with a known sensitivity or allergy to niacin. Persons with heart disease, particularly those who have recurrent chest pain (angina) or who recently suffered a heart attack, should take niacin only under the supervision of a physician. Persons taking high blood pressure or cholesterol-lowering drugs should contact a physician before taking niacin because of possible interactions. Do not take niacin unless recommended by and taken under the supervision of a physician if you have any of the following conditions: gallbladder disease, gout, arterial bleeding, glaucoma, diabetes, impaired liver function, peptic ulcer, pregnancy or lactating women. Increased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500 mg or more of niacin.

Discontinue use and consult a physician immediately if any of the following symptoms occur: persistent flu-like symptoms (nausea, vomiting, a general "not well" feeling); loss of appetite; a decrease in urine output associated with dark-colored urine; muscle discomfort such as tender, swollen muscles or muscle weakness; irregular heartbeat; or cloudy or blurry vision.

Keep out of reach of children.

INGREDIENTS

250 mg niacin (nicotinic acid), supplying 1,250% of the Reference Daily Intake (RDI) for niacin.

500 mg niacin (nicotinic acid), supplying 2,500% of the Reference Daily Intake (RDI) for niacin.

750 mg niacin (nicotinic acid), supplying 3,750% of the Reference Daily Intake (RDI) for niacin.

Each tablet also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red No. 40.

UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

Rev. 0198
40-00600

Call Upsher-Smith at: 1-800-654-2299

Top of Page

SCRIPTION
-Niacin® Tablets are manufactured utilizing a unique, patented polygel® controlled-release delivery system. This exclusive technology assures the gradual and measured release niacin (nicotinic acid) and is designed to reduce the incidence flushing and itching commonly associated with niacin use. lo-Niacin® Tablets are available in 250 mg, 500 mg, and 750 mg strengths.

SUGGESTED USE
Slo-Niacin® is a member of the vitamin B-complex group (nicotinic acid, vitamin B_3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

DIRECTIONS
Adults—one-half Slo-Niacin® Tablet morning or evening, or as directed by a physician.
Before using more than 500 mg daily, consult a physician.
Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.

Store at controlled room temperature, 15-30°C (59-86°F). Keep tightly closed.

CAUTION
Niacin may cause temporary flushing, itching and tingling, feelings of warmth and headache, particularly when beginning, increasing amount or changing brand of niacin. These effects seldom require discontinuing niacin use. Skin rash, upset stomach, and low blood pressure when standing are less common symptoms; if they persist, contact a physician.

Keep out of reach of children.

Rev. 0897
43-06411

3 0245-0064-11 4

PATENTED FORMULATION

SLO 750mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

List 0245-0064-11

WARNINGS
Slo-Niacin® Tablets should not be used by persons with a known sensitivity or allergy to niacin. Persons with heart disease, particularly those who have recurrent chest pain (angina) or who recently suffered a heart attack, should take niacin only under the supervision of a physician. Persons taking high blood pressure or cholesterol-lowering drugs should contact a physician before taking niacin because of possible interactions. Do not take niacin unless recommended by and taken under the supervision of a physician if you have any of the following conditions: gallbladder disease, gout, arterial bleeding, glaucoma, diabetes, impaired liver function, peptic ulcer, pregnancy or lactating women. Increased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500 mg or more of niacin.

Discontinue use and consult a physician immediately if any of the following symptoms occur: persistent flu-like symptoms (nausea, vomiting, a general "not well" feeling); loss of appetite; a decrease in urine output associated with dark-colored urine; muscle discomfort such as tender, swollen muscles or muscle weakness; irregular heartbeat; or cloudy or blurry vision.

EACH TABLET CONTAINS
750 mg niacin (nicotinic acid). Also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red No. 40.

EACH TABLET SUPPLIES
3,750% of the Reference Daily Intake (RDI) for niacin.

UPSHER-SMITH
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

U.S. Patents 5,126,145 and 5,268,181.

PATENTED FORMULATION

SLO 750mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

List 0245-0064-11

List 0245-0064-11

Doctor Recommended

SLO NIACIN®

polygel® controlled-release niacin

Dietary Supplement

750mg

100 Tablets

SLO 750mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

EXHIBIT #4

List 0245-0064-11

SLO NIACIN®

polygel® controlled-release niacin

Dietary Supplement

750mg

100 Tablets

3 0245-0064-11 4

Lot/Exp.

17375 1-00

Each Tablet Contains: 750 mg niacin (nicotinic acid). Also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red #40.

Each Tablet Supplies: 3,750% of the Reference Daily Intake (RDI) for niacin.

UPSHER-SMITH
UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447
 U.S. Patent No. 5,126,145 and other patents pending.
Rev. 0195 42-0641TA

Store at room temperature, 59°-86°F
Keep tightly closed.
PLEASE REFER TO PACKAGE INSERT FOR CAUTIONS AND WARNINGS.
Keep out of the reach of children.

DESCRIPTION

Slo-Niacin® Tablets are manufactured utilizing a unique, [illegible] polygel® controlled-release delivery system. This [illegible]sive technology assures the gradual and measured release of niacin (nicotinic acid) and is designed to reduce the incidence of flushing and itching commonly associated with niacin use. [illegible]acin® Tablets are available in 250 mg, 500 mg, and 750 [illegible]ngths.

SUGGESTED USE

Slo-Niacin® is a member of the vitamin B-complex group (nicotinic acid, vitamin B_3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

DIRECTIONS

Adults—one Slo-Niacin® Tablet morning or evening, or as directed by a physician.

Before using more than 500 mg daily, consult a physician.

Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.

Store at controlled room temperature, 15-30°C (59--86°F). Keep tightly closed.

CAUTION

Niacin may cause temporary flushing, itching and tingling, feelings of warmth and headache, particularly when beginning, increasing amount or changing brand of niacin. These effects seldom require discontinuing niacin use. Skin rash, upset stomach, and low blood pressure when standing are less common symptoms; if they persist, contact a physician.

out of reach of children.

Rev. 0897
43-06311

3 0245-0063-11 7

PATENTED FORMULATION

SLO 500mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

List 0245-0063-11

WARNINGS

Slo-Niacin® Tablets should not be used by persons with a known sensitivity or allergy to niacin. Persons with heart disease, particularly those who have recurrent chest pain (angina) or who recently suffered a heart attack, should take niacin only under the supervision of a physician. Persons taking high blood pressure or cholesterol-lowering drugs should contact a physician before taking niacin because of possible interactions. Do not take niacin unless recommended by and taken under the supervision of a physician if you have any of the following conditions: gallbladder disease, gout, arterial bleeding, glaucoma, diabetes, impaired liver function, peptic ulcer, pregnancy or lactating women. Increased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500 mg or more of niacin.

Discontinue use and consult a physician immediately if any of the following symptoms occur: persistent flu-like symptoms (nausea, vomiting, a general "not well" feeling); loss of appetite; a decrease in urine output associated with dark-colored urine; muscle discomfort such as tender, swollen muscles or muscle weakness; irregular heartbeat; or cloudy or blurry vision.

EACH TABLET CONTAINS

500 mg niacin (nicotinic acid). Also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red No. 40.

EACH TABLET SUPPLIES

2,500% of the Reference Daily Intake (RDI) for niacin.

UPSHER-SMITH

UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

U.S. Patents 5,126,145 and 5,268,181.

PATENTED FORMULATION

SLO 500mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

List 0245-0063-11

Doctor Recommended

SLO NIACIN®

polygel® controlled-release niacin

Dietary Supplement

500mg

100 Tablets

SLO 500mg NIACIN®

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

List 0245-0063-11

polygel® controlled-release niacin

Dietary Supplement 100 Tablets

PATENTED FORMULATION

SLO 500mg NIACIN®

List 0245-0063-11

the vitamin B-complex group (nicotinic acid, vitamin B_3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

Directions: Adults—one Slo-Niacin® Tablet morning or evening, or as directed by a physician. Before using more than 500 mg daily, consult a physician.

Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.

Store at controlled room temperature, 15-30°C (59-86°F).

Keep tightly closed.

PLEASE REFER TO PACKAGE INSERT FOR CAUTIONS AND WARNINGS.

Keep out of reach of children.

(nicotinic acid). Also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red No. 40.

Each Tablet Supplies: 2,500% of the Reference Daily Intake (RDI) for niacin.

UPSHER-SMITH

UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

U.S. Patents 5,126,145 and 5,268,181.
Rev. 1097 42-06311A

SLO NIACIN®

polygel® controlled-release niacin

Dietary Supplement

500mg

100 Tablets

3 0245-0063-11 7

Lot/Exp.

17828 9-00

EXHIBIT #5

PATENTED FORMULATION

Doctor Recommended

SLO NIACIN

polygel® controlled-release niacin 250mg

Dietary Supplement

SLO NIACIN®

Doctor Recommended

polygel® controlled-release niacin

Dietary Supplement

List 0245-0062-11

SLO NIACIN® 250mg

polygel® controlled-release niacin

Dietary Supplement **100 Tablets**

3 0245-0062-11 0

Keep out of the reach of children.

UPSHER-SMITH

EXHIBIT #6

Lot/Exp.

16514 11-98

DESCRIPTION

Slo-Niacin® Tablets are manufactured utilizing a unique, patented polygel® controlled-release delivery system. This exclusive technology assures the gradual and measured release of niacin (nicotinic acid) and is designed to reduce the incidence of flushing and itching commonly associated with niacin use. Slo-Niacin® Tablets are available in 250 mg, 500 mg, and 750 mg strengths.

SUGGESTED USE

Slo-Niacin® is a member of the vitamin B-complex group (nicotinic acid, vitamin B_3) and is suggested as a dietary supplement. This product has the advantage of a slower release of niacin than conventional dosage forms. This may permit its use by those who do not tolerate immediate-release tablets.

DIRECTIONS

250 mg: Adults — one Slo-Niacin® Tablet morning or evening, or as directed by a physician.

500 mg: Adults — one Slo-Niacin® Tablet morning or evening, or as directed by a physician.

750 mg: Adults — one-half Slo-Niacin® Tablet morning or evening, or as directed by a physician.

Before using more than 500 mg daily, consult a physician.

Note: Slo-Niacin® Tablets may be broken on the score line, but should not be crushed or chewed. The inactive matrix of the tablet is not absorbed and may be excreted intact in the stool.

Store at controlled room temperature, 15-30° C (59-86° F).

CAUTION

Niacin may cause temporary flushing, itching and tingling, feelings of warmth and headache, particularly when beginning, increasing amount or changing brand of niacin. These effects seldom require discontinuing niacin use. Skin rash, upset stomach, and low blood pressure when standing are less common symptoms; if they persist, contact a physician.

SLO-NIACIN®
Tablets
(polygel® controlled-release niacin)
Dietary Supplement
250, 500, and 750 mg

WARNINGS

Slo-Niacin® Tablets should not be used by persons with a known sensitivity or allergy to niacin. Persons with heart disease, particularly those who have recurrent chest pain (angina) or who recently suffered a heart attack, should take niacin only under the supervision of a physician. Persons taking high blood pressure or cholesterol-lowering drugs should contact a physician before taking niacin because of possible interactions. Do not take niacin unless recommended by and taken under the supervision of a physician if you have any of the following conditions: gallbladder disease, gout, arterial bleeding, glaucoma, diabetes, impaired liver function, peptic ulcer, pregnancy or lactating women. Increased uric acid and glucose levels and abnormal liver function tests have been reported in persons taking daily doses of 500 mg or more of niacin. Discontinue use and consult a physician immediately if any of the following symptoms occur: persistent flu-like symptoms (nausea, vomiting, a general "not well" feeling); loss of appetite; a decrease in urine output associated with dark-colored urine; muscle discomfort such as tender, swollen muscles or muscle weakness; irregular heartbeat; or cloudy or blurry vision.

Keep out of reach of children.

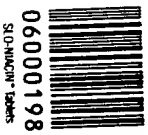
INGREDIENTS

250 mg niacin (nicotinic acid), supplying 1,250% of the Reference Daily Intake (RDI) for niacin.

500 mg niacin (nicotinic acid), supplying 2,500% of the Reference Daily Intake (RDI) for niacin.

750 mg niacin (nicotinic acid), supplying 3,750% of the Reference Daily Intake (RDI) for niacin.

Each tablet also contains: cellulose polymer derivative, vegetable stearine, magnesium stearate, silicon dioxide, glyceryl behenate, and FD&C Red No. 40.



SLO-NIACIN®
Tablets
(polygel® controlled-release niacin)
Dietary Supplement
250, 500, and 750 mg

UPSHER-SMITH

UPSHER-SMITH LABORATORIES, INC.
Minneapolis, MN 55447

U.S. Patents 5,126,145 and 5,268,181
Rev. 0198

40-00600

EXHIBIT #7

EXHIBIT #8

Efficacy and Safety of Controlled-Release Niacin in Dyslipoproteinemic Veterans

David R. Gray, PharmD; Timothy Morgan, MD; Steven D. Chretien, PharmD; and Moti L. Kashyap, MD

■ *Objective:* To evaluate the safety and efficacy of controlled-release niacin in patients with hyperlipoproteinemia.

■ *Design:* A retrospective cohort study.

■ *Setting:* A Department of Veterans Affairs Medical Center.

■ *Patients:* A consecutive sample of 969 predominantly elderly male veterans treated for dyslipoproteinemia with controlled-release niacin between October 1988 and October 1991.

■ *Main Outcome Measures:* Primary outcomes were lipid levels and lipoprotein cholesterol response, alterations in levels of hepatic enzymes and blood chemistry test results, and characterization of niacin-induced hepatotoxicity abstracted from the patient's medical, laboratory, and pharmacy records.

■ *Results:* 93% (896 of 969) of the cohort was evaluable. Patients (age, 61.7 years [9.4 years], mean [SD]) were treated for 1 to 36 months (13.0 months [9.7 months]) with an average maintenance dose of 1.67 g/d (0.8 g/d). Niacin was discontinued in 48.5% (435 of 896) of the patients primarily because of adverse effects. Poor glycemic control led to discontinuation in 40.6% (43 of 106) of the patients with diabetes mellitus. The lipoprotein response was dose-related and favorable (levels of total cholesterol, −19.1%; low-density lipoprotein cholesterol, −24.0%; high-density lipoprotein cholesterol, +5.7%; and triglycerides, −32.5%). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (aspartate aminotransferase, +29%; alanine aminotransferase, +23%; alkaline phosphatase, +25%; and glucose, +7%; $P = 0.0001$). Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for probable and for possible or probable niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease, and concurrent oral sulfonylurea therapy.

■ *Conclusions:* Controlled-release niacin is effective in treating dyslipoproteinemia in selected middle-aged and elderly veterans, but approximately one half of patients discontinued the drug because of adverse effects or other causes including noncompliance. Niacin should be avoided in patients with hepatic dysfunction or a history of liver disease, patients with diabetes mellitus, and patients who abuse alcohol. Because controlled-release niacin seems to be more potent than crystalline niacin, product substitution without dos adjustment should be avoided.

Ann Intern Med. 1994;121:252-258.

Niacin is an established antilipidemic agent that effectively decreases levels of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, very-LDL cholesterol, and triglycerides and increases levels of high-density lipoprotein (HDL) cholesterol (1, 2). Niacin has been shown to decrease mortality and the incidence of recurrent, nonfatal myocardial infarction in men and, in combination with bile acid–binding resins, to prevent or cause regression of atherosclerotic plaques (3, 4). Although niacin has been recommended as a first-line agent in the treatment of hyperlipidemic disorders (5), frequent adverse effects have limited patient and physician acceptance (6, 7). Sustained-release dosage forms of niacin appear to be better tolerated than regular niacin and, although more expensive, are much less costly than other antilipidemic agents. Recently, questions have been raised about the efficacy, tolerability, and risk for hepatotoxicity of niacin, especially the extended-release form. Hepatotoxicity is believed to be dose-related, usually with doses exceeding 3 g/d (8). The preponderance of evidence for increased hepatic dysfunction associated with extended-release niacin is based on a small number of anecdotal case reports (9–14), primarily in patients who were tolerating regular niacin before being switched to the extended-release preparation. New evidence from a double-blind parallel comparison (15) indicates that a sustained-release dosage form of niacin was hepatotoxic when compared with an immediate-release dosage form.

Clinical evaluation of the safety and efficacy of sustained-release niacin is limited. Regular niacin appeared to be slightly more effective in decreasing total cholesterol levels (6); however, direct comparisons of the lipid-lowering capability could not be made because of differences in doses actually consumed. The hypocholesterolemic effects of regular and extended-release niacin were similar in two uncontrolled studies (10, 16). A recent, randomized, controlled clinical trial showed that relatively low

SI Units

Normal Range	Conversion Factor
High-density lipoprotein cholesterol	mg/dL × 0.02586 = mmol/L
Low-density lipoprotein cholesterol	mg/dL × 0.02586 = mmol/L
Triglycerides	mg/dL × 0.01129 = mmol/L

Drugs

Generic Name	Brand Name
niacin	Slo-Niacin

Abbreviations

ALT alanine aminotransferase
AST aspartate aminotransferase
HDL high-density lipoprotein
LDL low-density lipoprotein

doses of wax-matrix sustained-release niacin were effective treatment for hypercholesterolemia (17).

The Department of Veterans Affairs Medical Center, Long Beach, California, has been active in implementing accepted guidelines (5) for the detection and treatment of hypercholesterolemia, and, in keeping with these guidelines, niacin has been extensively promoted and used as a first-line agent. This pharmacoepidemiologic study is a retrospective descriptive analysis of all patients treated with controlled-release niacin during a 36-month period. We describe the safety and efficacy of controlled-release niacin in a sample of predominantly male veterans treated for lipid disorders.

Methods

The medical records, laboratory records, and pharmacy prescription records were reviewed for all patients initiated on controlled-release niacin (Slo-Niacin; Upsher-Smith, Minneapolis, Minnesota) between October 1988 and April 1991, with data collection continuing to October 1991. Demographic characteristics and social, medical, and medication history were collected from the patients' medical and prescription records. Those patients with evaluable lipid profiles had lipoprotein phenotypes defined (for this study) as follows: phenotype IIa, LDL cholesterol level of 3.36 mmol/L (130 mg/dL) or more and triglyceride level of less than 2.82 mmol/L (250 mg/dL); type IIb, LDL cholesterol level of 3.36 mmol/L (130 mg/dL) or more and triglyceride level of 2.82 to 4.50 mmol/L (250 to 399 mg/dL); type IV, LDL cholesterol level of less than 3.36 mmol/L (130 mg/dL) and triglyceride level of 2.82 to 4.50 mmol/L (250 to 399 mg/dL) or a triglyceride level of 4.52 to 11.28 mmol/L (400 to 999 mg/dL); and type V, triglyceride level of 11.29 mmol/L (1000 mg/dL) or more. Active liver disease was defined as any one of the following: 1) increases in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase that were 1.5-fold or more than the upper limits of normal; 2) histologic evidence of fibrosis or cirrhosis; 3) evidence of decompensated liver disease; 4) positive test results for hepatitis B surface antigen; or 5) positive serologic test results for anti-hepatitis C. A history of liver disease was defined as previous disease (for example, jaundice, abnormal liver test results, ascites) but no current abnormal levels of liver enzymes and no histologic evidence of liver disease.

Lipid profile; levels of hepatic enzymes including ALT, AST, γ-glutamyltransferase, and alkaline phosphatase; and levels of glucose, uric acid, and albumin were recorded at baseline, at the end of each dose titration, and at the end of the study (the last levels were obtained while the patients were receiving controlled-release niacin). Liver enzyme levels, blood biochemistry test results, and lipid levels (18, 19) were measured by standard enzymatic methods. Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula but were not estimated for patients who had triglyceride levels of 4.52 mmol/L (400 mg/dL) or more. The laboratory participates with the Centers for Disease Control and Prevention Program for standardization of laboratory tests.

Those patients identified in the medical record as having niacin-induced hepatic dysfunction as well as those patients with increased levels of AST or ALT that were threefold or more than the upper limit of normal or increased levels of alkaline phosphatase that were twofold or more than the upper limit of normal were evaluated for causality with controlled-release niacin using the Naranjo nomogram (20). This probability scale for adverse drug reactions is based on a series of ten scored questions that evaluate the relation between an adverse event and a suspected drug. Based on this probability scale, the likelihood of a positive association between controlled-release niacin and liver dysfunction was classified into four categories: doubtful reaction—"likely related to factors other than a drug" (20); possible reaction—"followed a temporal sequence after a drug, possibly followed a recognized pattern to the suspected drug, and could be explained by characteristics of the patient's disease" (20); probable reaction—could not reasonably be explained by other causes; and definite reaction—confirmed by dechallenge and rechallenge of the suspected drug.

Blood lipid values, liver function test results, and standard biochemistry test results comparing baseline levels with those at the time of the final maintenance dose were analyzed by the Student paired *t*-test. Risk factor assessment of niacin-associated hepatic dysfunction was analyzed by chi-square analysis.

Table 1. Baseline Characteristics of Study Patients

Variable	Value
Patients, *n*	896
Age, *y*	61.7 ± 9.4*
Weight, *kg*	85.5 ± 15.2*
Men:women	850:46
Race, *n* (%)	
White	683 (76.2)
Black	117 (13.1)
Hispanic	70 (7.8)
Asian	10 (1.1)
Other	16 (1.8)
Lipoprotein phenotype (evaluable), *n*	200
IIa	111
IIb	55
IV	27
V	7
Relative contraindications, *n* (%)	371 (41.4)
Diabetes mellitus	160 (17.9)
Peptic ulcer disease by history	127 (14.2)
Gout	84 (9.4)
Hyperuricemia (uric acid ≥ 535 μmol/L)†	65 (7.3)
Liver disease by history	22 (2.5)
Contraindications, *n* (%)	36 (4.0)
Active liver disease	26 (2.9)
Active peptic ulcer disease	10 (1.1)

* Mean ± SD
† To convert to mg/dL, divide by 59.48.

Results

Patient Characteristics

Data collection and analysis were completed in 92.5% (896 of 969) of eligible patients. Patients not included were those who transferred to other facilities, left the area, or were lost to follow-up. Baseline characteristics (Table 1) indicated that patients were predominantly white men older than 50 years of age. Lipoprotein phenotype could be determined in 22.3% of the patients; the type IIa phenotype was the most common. Relative and absolute contraindications to niacin prescribing (Table 1) occurred in 41.4% and 4.0% of the patients, respectively.

Instructions for dosage titration of controlled-release niacin were used in 30% (269 of 896) of the patients. The average daily dose was approximately 1.5 g with the final dose (1.67 g [0.8 g], mean [SD]) only 0.3 g greater than the initial dose (1.36 g [0.7 g]). The number of dose adjustments for controlled-release niacin ranged from 0 to 5 (0.86 [1.0], mean [SD]). Colestipol (168 patients) was the most frequently prescribed additive antilipidemic agent, followed by gemfibrozil (33 patients) and lovastatin (11 patients). Data were insufficient to assess hepatic dysfunction in patients receiving lovastatin and controlled-release niacin concurrently. Approximately one half (461 of 896) of the patients were still receiving controlled-release niacin at the end of the survey period. Of the 435 patients no longer taking controlled-release niacin, 249

Table 2. Blood Lipid Values at Baseline and during Treatment with Controlled-Release Niacin*

Variable	Baseline	Final Maintenance	Mean Paired Difference (95% CI)	P Value†
	mg/dL (mmol/L)			
Total cholesterol	293.1 (7.58)	237.0 (6.13)	−56.1 (−50.0 to −62.2)	0.0001
LDL cholesterol	203.0 (5.25)	154.3 (3.98)	−48.7 (−40.4 to −57.0)	0.0001
HDL cholesterol	45.1 (1.16)	47.7 (1.24)	+2.6 (+0.9 to +4.3)	0.0035
Triglycerides	307.9 (7.96)	207.9 (5.38)	−100.0 (−55.9 to −144.1)	0.0001

* HDL = high-density lipoprotein; LDL = low-density lipoprotein. Note that SI values are in parentheses.
† Paired *t*-test.

had 276 documented reasons for discontinuation. The primary documented reasons for discontinuation were adverse effects, of which flushing and itching (80 patients), increased blood glucose levels (43 patients), gastrointestinal complaints (33 patients), and increased hepatic enzyme levels (33 patients) were the most common. Of the 33 patients who discontinued controlled-release niacin because of gastrointestinal complaints, aspirin use was similar (15 of 33) to that of the group as a whole (549 of 896). Controlled-release niacin had to be restarted 46 times in 70 patients in the long-term cohort (treatment duration, 30 to 36 months); 24% of the treated patients discontinued controlled-release niacin by themselves for no apparent reason every year.

Lipoprotein Response

Blood lipid values at baseline compared with those at the final maintenance dose are summarized in Table 2. The overall lipoprotein response showed the expected decreases in total cholesterol (−19.1%), LDL cholesterol (−24.0%), and triglycerides (−32.5%) as well as increases in HDL cholesterol (+5.7%). Evaluable patients with mean changes in lipid levels in the long-term cohort (n = 70) were limited (total cholesterol, −27.8%, n = 35; LDL cholesterol, −29.3%, n = 11; HDL cholesterol, −0.2%, n = 14; and triglycerides, −53.2%, n = 13). For those patients in whom a complete lipid profile was available at baseline (n = 200), a 25.4% decrease was noted in levels of LDL cholesterol in patients with phenotype IIa compared with a 15.1% decrease in patients with phenotype IIb, a difference of 10.3% (95% CI, 3.3% to 17.3%; P = 0.004). Patients with HDL cholesterol levels of 1.03 mmol/L (40 mg/dL) or less at baseline had a 12.2% increase in HDL compared with a 3.2% increase in those with baseline levels more than 1.03 mmol/L (40 mg/dL), a difference of 9.0% (CI, 1.1% to 16.9%; $P < 0.03$). The relation between controlled-release niacin dose and changes in levels of plasma lipoprotein cholesterol is shown in Figure 1. A greater decrease in levels of mean total cholesterol and triglycerides was seen as the dose of niacin increased from 1.0 to 3.0 g/d (11.7% to 27.0% and 18.7% to 53.0%, respectively). The decrease in the mean level of LDL cholesterol was 12.1%, 26.2%, and 22.6% for niacin doses of 1.0, 2.0, and 3.0 g/d, respectively. The increase in levels of HDL cholesterol peaked at a niacin dose of 2.0 g/d (14.2%).

Blood Chemistry Test Results

Serum chemistry values at baseline compared with those at the final maintenance dose are summarized in Table 3. Levels of mean liver enzymes increased in a statistically significant manner over baseline but remained within the normal range. Mean changes in levels of hepatic enzymes were similar when comparing the entire cohort with the long-term cohort (AST levels, +29% compared with +33%; ALT levels, +23% compared with +20%; and alkaline phosphatase levels, +25% compared with +22%). A decrease in total cholesterol levels was associated with an increase in AST levels (r = −0.32, $P <$ 0.001) and also with a decrease in serum albumin levels (r = +0.31, $P < 0.001$). No change was seen in uric acid levels, although there was a 6.7% increase in glucose levels (P = 0.0001) and a 4.7% decrease in albumin levels (P = 0.0001). Overall, the average change in laboratory tests with controlled-release niacin was not clinically significant. The relation between controlled-release niacin dose and percentage change in liver enzyme levels is shown in Figure 2. Statistically but not clinically meaningful dose-related increases were found over a niacin dosage range of 1.0 to 3.0 g/d.

Of 160 patients with diabetes mellitus, 14 (4 with new-onset diabetes and 10 with diet-controlled diabetes) required the addition of oral hypoglycemic agents while on controlled-release niacin. Oral hypoglycemic agents were the most common mode of treatment (41.9%), followed by diet alone (36.2%) and insulin (21.9%). Controlled-release niacin was discontinued in 106 of 160 (66.3%) patients with diabetes because of poor glycemic control in 40.6% (43 of 106).

Hepatotoxicity

Forty-six patients met criteria for niacin-associated hepatotoxicity. The Naranjo ratings were classified as follows: 1 definite, 19 probable, 22 possible, and 4 doubtful. The doubtful patients were excluded from further analysis. Twenty of 896 (2.2%; CI, 1.4% to 3.4%) patients met biochemical criteria for probable niacin-induced hepatotoxicity, and 42 of 896 (4.7%; CI, 3.4% to 6.3%) patients met criteria for possible or probable niacin-induced hepatotoxicity.

Most reactions (30 of 42) were mild and resulted in biochemical changes that resolved after discontinuation of

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United States Patent [19]

Evenstad et al.

[11] Patent Number: 5,126,145

[45] Date of Patent: Jun. 30, 1992

[54] CONTROLLED RELEASE TABLET CONTAINING WATER SOLUBLE MEDICAMENT

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[21] Appl. No.: 536,184

[22] Filed: Jun. 11, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 337,460, Apr. 13, 1989, abandoned.

[51] Int. Cl.[5] A61K 9/20; A61K 9/22

[52] U.S. Cl. 424/465; 424/468; 424/469; 424/470; 424/488; 424/499; 424/502; 514/960; 514/964

[58] Field of Search 424/488, 469, 470, 465, 424/489

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Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

[57] ABSTRACT

A sustained or controlled release tablet is disclosed. The tablet comprises a water soluble medicament, a hydroxypropyl methylcellulose having sustaining action, a pharmaceutical binding agent, and a hydrophobic component.

24 Claims, 2 Drawing Sheets

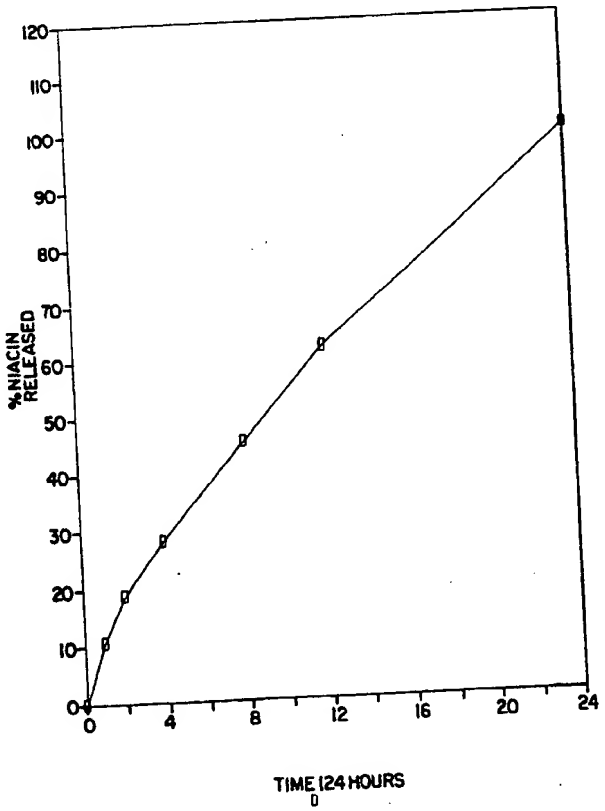
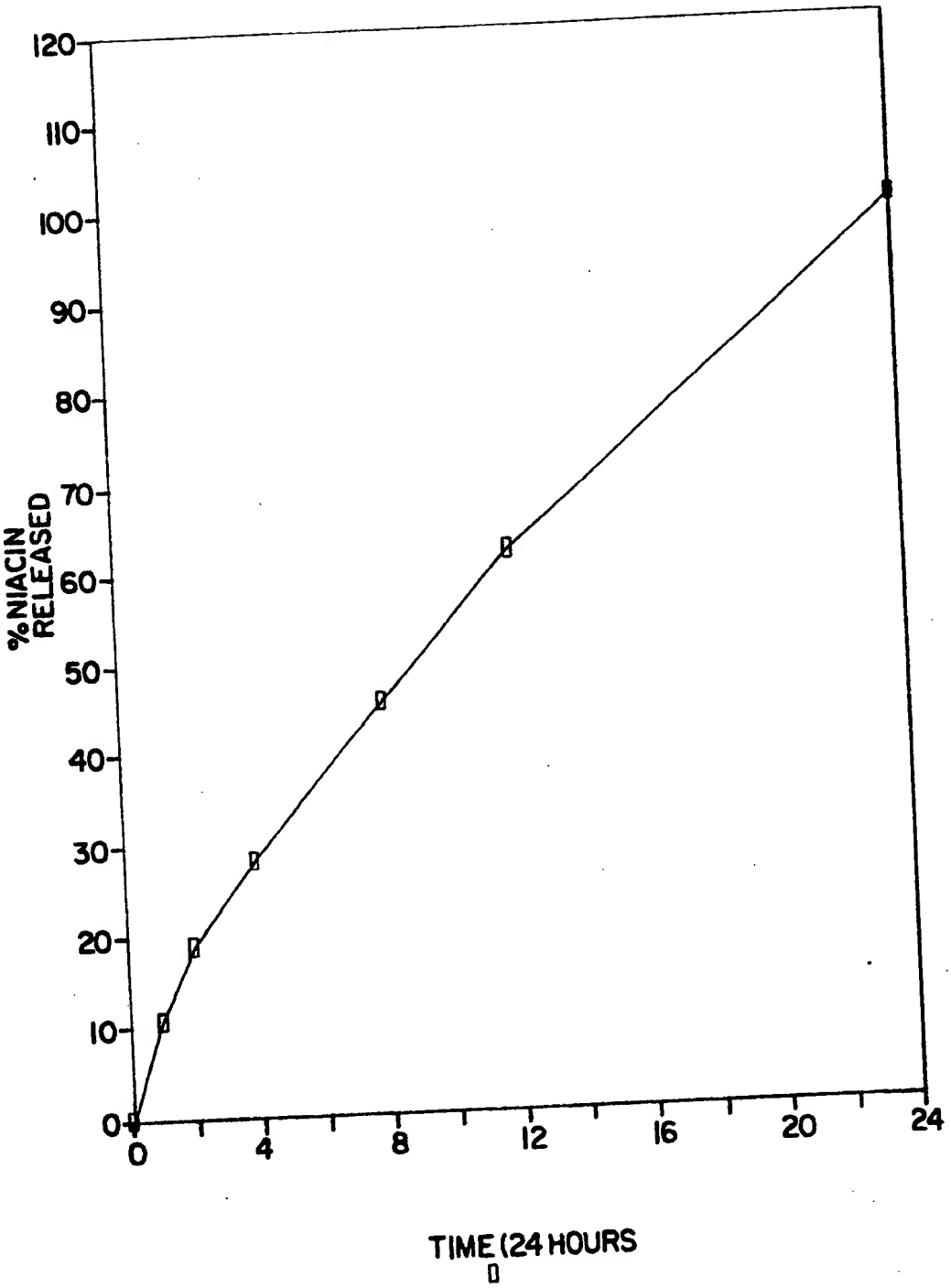


FIG. 1


120
110
100
90
80
70
60
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20
10
0
% NIACIN RELEASED
0
4
8
12
16
20
24
TIME (24 HOURS

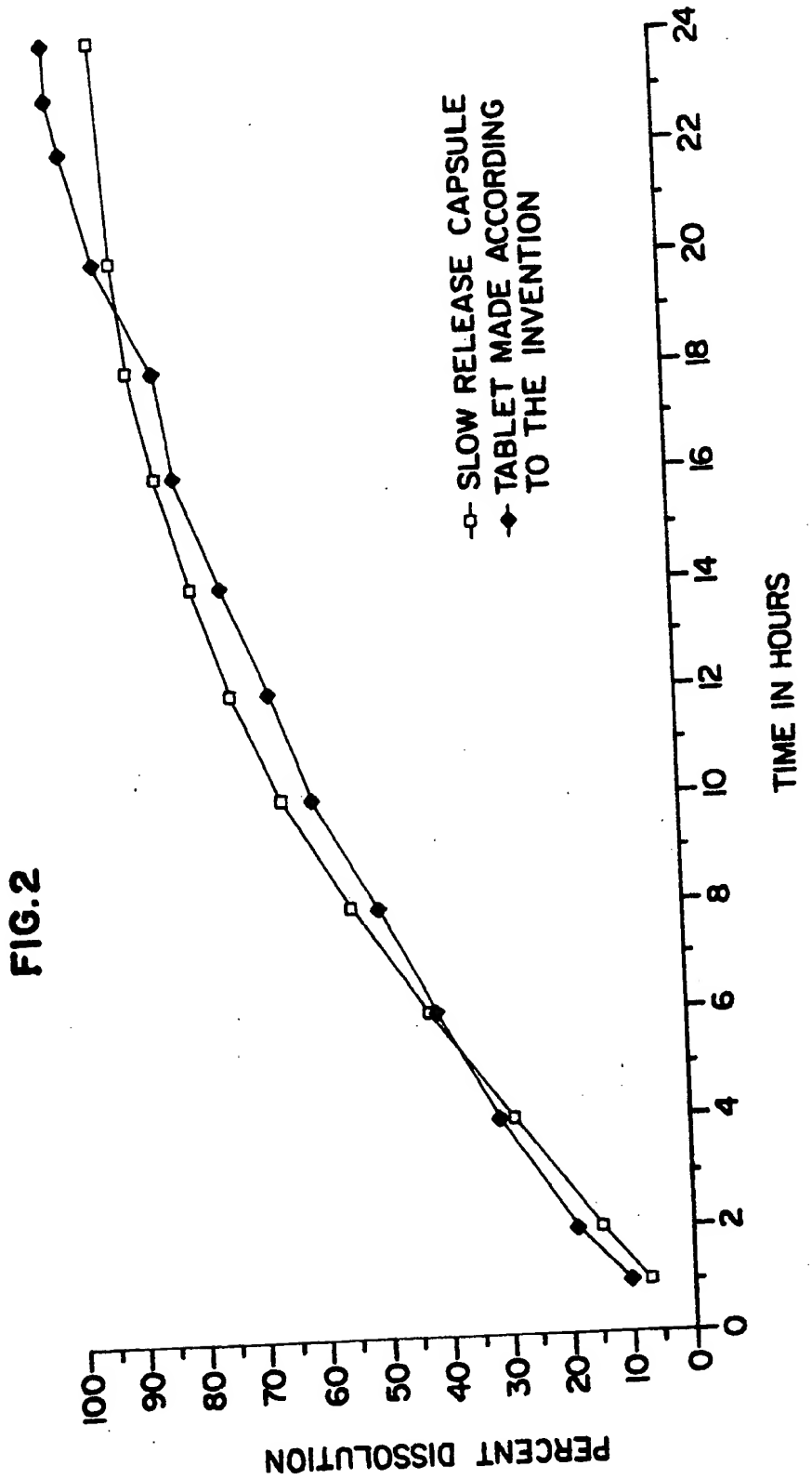
SLOW RELEASE CAPSULE
TABLET MADE ACCORDING TO THE INVENTION
PERCENT DISSOLUTION
TIME IN HOURS
0
2
4
6
8
10
12
14
16
18
20
22
24
10
20
30
40
50
60
70
80
90
100

FIG.2

CONTROLLED RELEASE TABLET CONTAINING WATER SOLUBLE MEDICAMENT

This is a continuation of application Ser. No. 07/337,460, filed Apr. 13, 1989 now abandoned.

This, invention relates to a controlled release tablet comprising hydroxypropyl methylcellulose, a binding agent. an internal hydrophobic component, and water soluble medicament. The tablet can be formed by wet granulation techniques.

BACKGROUND OF THE INVENTION

Sustained or controlled release products for oral administration are known and widely used. Hydroxypropyl methylcellulose has been used in such products. It is believed that hydroxypropyl methylcellulose in such tablets partially hydrates on the tablet surface to form a gel layer. The rate of hydration and gelling of the hydroxypropyl methylcellulose tablet surface affects the drug release from the tablet and contributes significantly to the sustained release aspect of such products.

However, it has been difficult to formulate controlled release tablets of soluble medicaments and hydroxypropyl methylcellulose. First, it has been difficult to achieve the desired dissolution profiles or to control the rate of release of soluble to freely soluble medicaments. This may be due to leaching of the medicament from the tablet before hydration and gelling of the hydroxypropyl methylcellulose occurs. Second, known tableting techniques such as direct compression and granulation may fail when a high proportion of soluble medicament is required regardless of its degree of solubility.

Bead coating technology can be used to form sustained release products. These products typically comprise hard gelatin capsules containing coated beads of medicament. Soluble medicaments are available in controlled release capsules of this type. However, tablets have certain advantages over capsules and these advantages are lost with the use of capsules for sustained release of soluble therapeutic agents.

Tablets have several advantages over capsules. For some drugs, it is recommended that the patient begin taking a smaller dose and gradually over time increase the dose to the desired level. This can help avoid undesirable side effects. Tablets can be preferable to capsules in this regard because a scored tablet easily can be broken to form a smaller dose.

In addition, tableting processes such as wet granulation are generally simpler and less expensive than bead coating and capsule formation. Further, tablets can be safer to use because they may be less subject to tampering.

Accordingly, a need exists for a controlled release product of more soluble medicaments, combining the advantages of hydroxypropyl methylcellulose in sustaining and controlling the release rate, the relative ease and low cost of wet granulation, and the other advantages of the tablet form over capsules.

BRIEF DESCRIPTION OF THE INVENTION

We have discovered a sustained release tablet comprising hydroxypropyl methylcellulose with sustaining properties but negligible binding properties, in an amount effective to produce a desired release rate, sufficient water soluble pharmaceutical binder to permit wet granulation, an amount of internal hydrophobic component effective to permit wet granulation. and a water soluble medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing an average dissolution profile of 750 mg. niacin tablets made in accordance with the invention.

FIG. 2 is a graph comparing the average dissolution profiles of niacin (500 mg) tablets made in accordance with the invention and a commercially available extended-release niacin (500 mg) capsule.

DETAILED DESCRIPTION OF THE E INVENTION

The controlled release tablet includes a medicament and a hydrophillic polymer matrix for achieving controlled or sustained or extended release of the medicament. The tablet can include a high proportion of water soluble medicament and can be prepared by standard wet granulation techniques. A desirable dissolution profile can be achieved. The tablet can be scored to permit easy titration up to the desired dose.

The medicament can be any suitable water soluble therapeutically active material which is commonly administered orally. The medicaments that we believe will benefit most from the invention are those that appear to be too soluble for ready inclusion in an effective controlled release tablet utilizing hydroxypropyl methylcellulose. The solubility of the medicaments could from about 0.1 to 30% (at 25° C.). This includes slightly soluble to freely soluble compounds, according to the definitions provided by Remington Pharmaceutical Sciences.

The minimum amount of medicament or active drug in the tablets of the invention will typically be about 30% by weight based on the weight of the tablet and can range up to about 90%. Within this range, generally it is possible to incorporate a greater amount of a less soluble medicament.

Niacin, with a water solubility of about 1.67 g/100ml (25° C.), is a medicament falling within the scope of the invention. Niacin has the chemical formula $C_6H_5NO_2$ and is also known as nicotinic acid. It is commercially available as fine white crystals or white crystalline powder, from sources such as Lonza and Ashland Chemical. It will typically be present at a level of from 50–85% by weight of the tablet. Other therapeutically active materials suitable for use in the invention include morphine sulfate, chlorpheniramine hydrochloride, pseudoephedrine, codeine sulfate and diltiazem hydrochloride, aspirin, acetaminophen, and naproxen.

The hydrophillic polymer matrix of the tablets of the invention is a dynamic system involving hydroxypropyl methylcellulose wetting, hydration, and dissolution. Other soluble excipients or drugs also wet, dissolve, and diffuse out of the matrix while insoluble materials are held in place until the surrounding polymer/excipient/-drug complex erodes or dissolves away.

The most significant mechanism by which drug release is controlled is through the use of hydroxypropyl methylcellulose. The hydroxypropyl methylcellulose, present throughout the tablet, partially hydrates on the tablet surface to form a gel layer. Overall dissolution rate and drug availability are dependent on the rate of soluble drug diffusion through the wet gel and the rate of tablet erosion. Hydroxypropyl methylcellulose with substitution rates of about 7–30% for the methoxyl group and greater than 7% or about 7–20% for the

hydroxypropoxyl group are preferred for formation of this gel layer. More preferred are substitution rates of 19–30% for the methoxyl group and 7–12% for the hydroxypropyl group.

Hydroxypropyl methylcelluloses vary in their viscosity, methoxy content, and hydroxypropoxyl content. Properties also vary. Some have more sustaining properties or the ability to achieve conrolled release of medicaments. Others have good binding properties and are less desirable for sustained properties. By "binding properties" we are referring to the ability to act as a binding agent for tablet production by wet granulation, for example, incorporating the hydroxypropyl methylcellulose into aqueous solution in order to spray onto the dry powders. Hydroxypropyl methylcelluloses with good sustaining properties are too viscous for use as the binder in wet granulation techniques.

The tablets of the invention comprise about 5–30 percent by weight hydroxypropyl methylcellulose with sustaining properties and negligible binding properties. Such hydroxypropyl methylcelluloses generally have a viscosity of no less than about 1000 centipoises.

More typically, the viscosity will be no less than about 4000 cps. For improved performance, the tablet will comprise about 5–20 weight percent, or, more preferably, about 8–12 percent hydroxypropyl methylcellulose with sustaining characteristics.

A preferred hydroxypropyl methylcellulose with sustaining properties is a hydroxypropyl methylcellulose with substitution type 2208, with a nominal viscosity, 2% aqueous, of about 100,000 cps, a methoxyl content of about 19–24%, and a hydroxypropoxyl content of about 7–12%. A "controlled release" grade is preferred, with a particle size where at least 90% passes through a #100 USS mesh screen. A commercially-available hydroxypropyl methylcellulose meeting these specifications is the Methocel K100MCR, from The Dow Chemical Company.

The tablet further comprises or includes about 2–15 weight percent water soluble pharmaceutical binder. The binder or binding agent aids in tablet production by wet granulation, serving as an adhesive and adding strength to the tablet.

Many suitable binders are known. They include polyvinyl pyrollidone, starch, gelatin, sucrose, lactose, methylcellulose, hydroxypropyl methylcellulose, and the like. For good binding action without excess binding agent, we prefer the use of about 2–8% by weight, or more preferably, particularly where the preferred binding agent is used, about 2–5% by weight.

The preferred water soluble pharmaceutical binder for use in this invention is hydroxypropyl methylcellulose having binding properties. Such hydroxypropyl methylcelluloses typically have a much lower viscosity than the hydroxypropyl methylcelluloses that have good sustaining characteristics. Generally, the viscosity of a 2% aqueous solution will be less than about 1000 cps. More typically, it will be less than 100 cps.

A preferred hydroxypropyl methylcellulose for use as a binding agent in the context of the invention has a nominal viscosity, 2% aqueous, of about 15, a methoxy content of about 28–30%, a hydroxypropyl content of about 7–12%, and a particle size of 100% through USS 30 mesh screen and 99% through USS 40 mesh screen. Hydroxypropyl methylcellulose 2910, Methocel E15 from The Dow Chemical Company meets these standards and is a preferred binder.

Other suitable binding hydroxypropyl methylcelluloses include Methocel ESLVP, Methocel E50LVP, and Methocel K3P. The methylcellulose Methocel AISLVP can also be used.

Another binder we recommend is polyvinyl pyrollidone, also known as polyvidone, povidone, and PVP. Typical properties of commercially available PVP's include density between 1.17 and 1.18 g/ml and an average molecular weight ranging from about 10,000 to 360,000. Generally, the higher molecular weight PVP's would be more suitable for use in this invention. Suppliers include BASF Wyandotte and GAF.

An essential component of the invention is what we refer to as the hydrophobic component. This component permits wet granulation of soluble medicaments with hydroxypropyl methylcellulose where it would not otherwise be easily accomplished using standard wet granulation techniques. In the absence of this component, we have found that the hydroxypropyl methylcellulose/medicament mixture tends to become "doughy" and granules or powder cannot easily be obtained.

The hydrophobic component comprises a wax-like material. The wax-like material comprises a solid generally insoluble substance having a waxy consistency. It should, of course, be ingestible. Many such materials are known and include waxes such as beeswax, carnauba wax, candelilla wax, Japan wax, paraffin, hydrogenated castor oil, higher fatty acids, such as palmitic acid, stearic acid, and myristic acid, esters of such higher fatty acids such as substituted mono-, di-, and tri-glycerides, acetylated monoglycerides, glyceryl monostearate, glyceryl tristearate, cetyl palmitate, glycol stearate, glyceryl tri-myristate, higher fatty alcohols such as cetyl alcohol, stearyl alcohol, and myristyl alcohol, and mixtures thereof.

Two wax-like materials are preferred in view of their ready availability in powdered form, reasonable cost, ease of handling, and their effectiveness in the context of this invention. These waxy materials are hydrogenated vegetable oil and stearic acid. Hydrogenated vegetable oil generally consists mainly of the triglycerides of stearic and palmitic acids, and is readily commercially available. A preferred hydrogenated vegetable oil for use in this invention is available through Edward Mendell, Co., Inc., of N.Y., under the trademark Lubritab ®. The Lubritab ® product has a bulk density of 0.48–0.56 grams per milliliter, a melting point of from 61°–66° C., a saponification value of 188–198, 0.8 maximum unsaponifiable matter, and a typical particle size distribution of 15 percent maximum on 100 mesh USS screen, 35 percent maximum through 200 mesh USS screen. An advantage of this product is its availability in powder form. A similar hydrogenated vegetable oil is available from Durkee, under the trademark Duratex.

Stearic or octadecanoic acid is typically manufactured from fats and oils derived from edible sources, and commercial stearic acid is typically a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid $C_{16}H_{32}O_2$). Stearic acid is available from many chemical suppliers, including Emery Industries and Mallinckrodt, Inc.

The powdered stearic acid NF available from Mallinckrodt contains not less than 40.0 percent $C_{18}H_{36}O_2$ and not less than 40.0 percent $C_{16}H_{32}O_2$; the sum of these two components is not less than 90.0 percent. The congealing temperature is not lower than 54°, and the iodine value is not more than 4.

The hydrophobic component should be present in an amount effective to permit wet granulation of the controlled release tablet. Such an amount is commonly 2–20 percent by weight of the tablet depending on the solubility of the medicament. Higher concentrations will be required for more soluble medicaments. Preferably, for good granulating results and sustained release, it will be present at from 5–15 percent of the total tablet weight, or more preferably, 6–12 percent by weight.

Other components commonly used in tablet formation, such as external lubricants, dyes, fillers and extenders, may also be used as desired. External lubricants or tableting aids can include calcium stearate, stearic acid, hydrogenated vegetable oils, talc, corn starch, colloidal silicone dioxide, magnesium stearate, and glyceryl behenate. We have found that a combination of glyceral behenate, magnesium stearate, and colloidal silicon dioxide is particularly effective as a tableting aid.

The external lubricants, typically added to the dried granules before tableting, if used, can be present at up to about 5 percent of the total tablet weight. More preferably, they will be present at 0.5–4 percent, or for improved tableting, 1–3 percent of the tablet weight.

Dyes can, of course, be used for a more pleasing tablet appearance. Many suitable ingestible dyes for tablets are known and are widely available.

Fillers or extenders can be used if needed or desired. When a tablet containing a 250, 500, or 750 mg. dose of niacin is formed, fillers or extenders typically would not be used because the medicament itself supplies sufficient volume to the tablet. However, fillers or extenders may be desirable where a lower dose of medicament is used. Many fillers or extenders are known and are readily available, including calcium sulfate, dicalcium phosphate, tricalcium phosphate, lactose, sucrose, starch dextrose, and microcrystalline cellulose.

The methods of forming the tablets of the invention are typical wet granulation methods, either conventional or fluid bed. A uniform blend of the hydrophobic component (flakes or powder) and dye, if used, is formed. The binding agent is dissolved in water to form a binding agent solution. The hydrophobic component blend, the sustaining hydroxypropyl methylcellulose, and the medicament are granulated using the binding agent solution to a final moisture level of less than about 7 percent, preferably less than about 5 percent. In the conventional process, the granulation is removed from the mixer and oven dried. External lubricating agents are then mixed in and the mixture is tableted. As would be understood by one of skill in the art, fluid bed processing would not require the oven drying step; instead the components would be granulated and dried in one procedure.

Where niacin is the medicament, useful tablets include doses of 250, 500, and 750 mg. High doses such as 750 mg. can cause side effects such as uncomfortable flushing and nausea unless treatment begins with smaller doses. Tablets can be scored to permit dasy breakage into smaller doses for titration up to the standard 750 mg. dose given twice daily. Titration, particularly with sustained release tablets, has been shown to help avoid side effects of niacin therapy.

Tablets made according to the invention can have desirable dissolution profiles mimicking zero order absorption characteristics or constant rate of release over time. Niacin tablets in accordance with the invention show dissolution profiles of 10–35% in 2 hours after ingestion, 40–70% in 8 hours, and at least 90% dissolution in 24 hours. Even more preferably, the profile of the niacin tablets is 10–30% release in 2 hours, 40–60% in 8 hours, and complete dissolution in 24 hours, and tablets in accordance with the invention have shown this profile.

The invention will be further understood by reference to the following Examples which include preferred embodiments.

EXAMPLE I

750 mg. niacin tablets were formed having the following components:

	% by Weight	Mg./Tablet
Niacin (Lonza)	73.07	750.0
Hydroxypropyl Methylcellulose 2910 (Methocel E15LV, Dow)	2.50	25.7
Hydroxypropyl Methylcellulose 2208 (Methocel K100MCR, Dow)	9.74	100.0
Hydrogenated Vegetable Oil (Lubritab, Mendell)	11.56	118.7
Glyceryl Behenate (Compritol 888)	0.50	5.1
Magnesium Stearate (Mallinckrodt)	1.50	15.4
FD&C Red #40 Lake Dye (40%) (Colorcon)	0.13	1.3
Colloidal Silicon Dioxide (Syloid 244)	1.00	10.3

To form the tablest, 16 liters of water was heated to 95° C. in a stainless steel container. The Methocel E15LV powder was slowly added while mixing until a homogenous suspension was obtained. The impeller speed was adjusted to avoid excessive air from entering the solution through the vortex.

48 liters of very cold water was slowly added and the mixture was mixed thoroughly until a clear solution was obtained and the temperature was below 20° C. Mixing continued for an additional 20 minutes.

The hydrogenated vegetable oil was sized through a USS No. 16 screen and added to a mixer. The dye was added to the mixer and mixed until the color distribution was uniform, about 5 minutes. The color mix was then transferred to a ribbon blender. The niacin powder was added to the ribbon blender and mixed for about 10 minutes. The Methocel K100MCR was then added and mixed for an additional 10 minutes.

The Methocel E15LV solution was sprayed in and then mixed for 1 minute. The resulting wet granulation was then sized through a USS No. 16 screen.

The sized wet granulation was spread lightly on trays, at approximately 2 kilograms per tray. The granulation was dried in an oven at 230° F. to a moisture content of less than 5 percent. The oven dried granulation was then sized through a USS No. 12 screen. After sizing, the granulation was collected in double poly-lined drums.

Three approximately 200 kilogram batches were formed in the above manner, each utilizing 149.06 kilograms niacin, 3.97 kilograms Methocel E15LV, 19.87 kilograms Methocel K100MCR, 24.84 kilograms Lubritab hydrogenated vegetable oil, and 0.26 kilograms FD&C Red Dye #40 Lake 40% pure dye. These batches were weighed, and combined in a ribbon blender. 3.0 kilograms glyceryl behenate and 3.0 kilograms magnesium stearate were then added to the ribbon blender and the mixture was mixed for 5 minutes.

The resulting product was tableted using a standard rotary press into tablets of 750 milligrams niacin.

EXAMPLE II

750 milligram niacin tablets were formed as follows:

Per Part	Milligrams/ Tablet	Kilograms Used
Niacin (Lonza)	750.00	312.500
Hydroxypropyl Methylcellulose 2910 (Methocel E15LV, Dow)	24.00	10.000
Hydroxypropyl Methylcellulose 2208 (Methocel K100MCR, Dow)	94.10	39.200
Hydrogenated Vegetable Oil (Lubritab, Mendell)	62.40	26.00
FD&C Red #40 Lake Dye (40%) (Colorcon)	0.70	0.300

The niacin tablets of Example II were formulated by the fluid bed process. Half of the above quantities were used for the first granulation. In this granulation, 33.000 kilograms deionized water were added to a stainless steel steam kettle and heated to 95° C. While mixing (but avoiding excess foaming), the Methocel E15LV and dye were added to the water. 67.000 kilograms cold deionized water were then added and mixing continued for about 20 minutes. The mixture was cooled to 21° C.

To the fluid bed container were added the niacin. Methocel K100MCR, and Lubritab hydrogenated vegetable oil. These three components were granulated with the Methocel E15LV solution. After exhausting the granulating solution, the material in the fluid bed containers was dried to less than 1% moisture.

The dried material was transferred to clean polylined containers. Using the Sweco Sifter, fitted with a 12 mesh screen, the granulation was sized into clean polylined drums.

A second batch of granulation was formed in an identical manner using the remaining half of the components. The two granulations were then added to a ribbon blender. These components were blended for 5 minutes. 6.000 kilograms magnesium stearate, 2.000 kilogram glyceral behenate, and 4.000 kilograms colloidal silicon dioxide were added to the ribbon blender and mixed for 5 minutes. The material was transferred to clean poly-lined drums and later tableted into tablets containing 750.00 milligrams niacin.

Two other formulations are shown below.

EXAMPLE III

Chemical Name	Milligrams/Tab	Percent
Niacin	750.0	78.125
Methocel E15LV (hydroxypropyl methylcellulose)	24.0	2.50
Methocel K100MCR (hydroxypropyl methylcellulose)	94.1	9.80
Lubritab (hydrogenated vegetable oil)	62.4	6.50
FD&C Red #40 dye	0.7	0.075
Magnesium Stearate	14.4	1.50
Compritol (glyceryl behenate)	4.8	0.50
Syloid 244 (colloidal silicon dioxide)	9.6	1.00

Tablets having the formulation of example III were made using conventional and fluid bed granulating techniques in a production mode.

FIG. 1 shows the average dissolution pattern of six tablets having the formula shown in Example III.

Tablest were dissolved using a Hanson Dissolution Apparatus with a U.S.P. rotating bracket at 100 rpm in 900 ml. water at 37° C. Samples were taken from each dissolution vessel at 1, 2, 4, 8, 12, and 24 hours, and analyzed by UV for nicotinic acid content. The results show a desirable release pattern.

Chemical Name	Milligrams/Tab	Percent
Niacin	750.0	76.220
Methocel E15LV (hydroxypropyl methylcellulose)	24.0	2.439
Methocel K100MCR (hydroxypropyl methylcellulose)	94.1	9.561
Lubritab (hydrogenated vegetable oil)	86.4	8.780
FD&C Red #40 dye	0.7	0.073
Magnesium Stearate	14.4	1.463
Compritol (glyceryl behenate)	4.8	0.488
Syloid 244 (colloidal silicon dioxide)	9.6	0.976

Tablets having the formulation of Example IV were made using conventional granulating techniques in the laboratory.

Chemical Name	By Weight %	Mg./Tablet
Niacin	73.07	500.00
Methocel E15LV (hydroxypropyl methylcellulose)	2.50	17.11
Methocel K100MCR (hydroxypropyl methylcellulose)	9.74	66.65
Lubritab (hydrogenated vegetable oil)	11.56	79.10
Compritol 888 (glyceryl behenate)	0.50	3.42
Magnesium Stearate	1.50	10.26
FD&C Red #40 dye	0.13	.89
Syloid 244 (colloidal silicon dioxide)	1.00	6.84

Tablets having the composition shown in Example V were made using conventional and fluid bed techniques. The dissolution pattern of tablets made in accordance with the formula of Example V was compared with the dissolution pattern of a typical commercially available extended release capsule, 500 mg. niacin. Six samples of each product were dissolved using a Hanson Dissolution Apparatus with a U.S.P. rotating basket at 100 rpm in 900 ml. of water at 37° C. Samples were taken from each dissolution vessel over a 24-hour period, and analyzed by UV for nicotinic acid content. As shown in FIG. 3, the tablets of the invention followed by similar profile to the commercially available extended release capsules, 500 mg. niacin.

Chemical Name	By Weight % Total	Mg/Tablet
Niacin	73.07	250.00
Methocel E15LV (hydroxypropyl methylcellulose)	2.50	8.55
Methocel K100MCR (hydroxypropyl methylcellulose)	9.74	33.32
Lubritab (hydrogenated vegetable oil)	11.56	39.55
Compritol 888	0.50	1.71

-continued

Chemical Name	By Weight % Total	Mg/Tablet
(glyceryl behenate)	1.50	5.13
Magnesium Stearate	0.13	.45
FD&C Red #40 dye	1.00	3.42
Syloid 244 (colloidal silicon dioxide)		

Tablets having the composition shown in Example VI were made using conventional and fluid bed techniques.

The foregoing description and examples are illustrative of the invention. However, since persons skilled in the art can make various embodiments without departing from the spirit and scope of the invention, the invention is embodied in the claims hereafter appended.

We claim:

1. A controlled release uncoated tablet comprising:

(a) about 5–20 percent by weight hydroxypropyl methylcellulose having a viscosity of about 1000 or greater, a substitution rate for the methoxyl group of about 7–30% and a substitution rate for the hydroxypropoxyl group of about 7–20%;

(b) about 2–8 percent by weight hydroxypropyl methylcellulose having a viscosity of less than about 1000, methyl cellulose, or polyvinyl pyrollidone;

(c) about 5–15 percent by weight hydrogenated vegetable oil or stearic acid; and

(d) a therapeutically active material having a water solubility of about 0.1–30% at normal room temperature;

wherein said tablet has a dissolution profile, with a substantially zero order absorption characteristic, of about 10–35% within 2 hours after ingestion.

2. A controlled release uncoated tablet comprising:

(a) about 5–30 percent by weight hydroxypropyl methylcellulose with sustaining properties;

(b) about 2–15 percent by weight water soluble pharmaceutical binder;

(c) about 2–20 percent by weight hydrophobic component; and

(d) a medicament having a solubility of about 0.1 to 30 wt-% in water;

wherein said tablet has a dissolution profile, with a substantially zero order absorption characteristic, of about 10–35% within 2 hours after ingestion.

3. The controlled release tablet of claim 2 wherein the water soluble medicament comprises niacin and forms about 50–85 percent by weight of the tablet.

4. The controlled release tablet of claim 2 wherein the hydroxypropyl methylcellulose comprises a hydroxypropyl methylcellulose having a nominal viscosity, 2 percent aqueous solution, of about 100,000 cps, a methoxyl content of about 19–24 percent, a hydroxypropoxyl content of about 7–12 percent, and a particle size where at least 90 percent passes through a USS 100 mesh screen.

5. The controlled release tablet of claim 2 wherein the water soluble pharmaceutical binder is selected from the group consisting of hydroxypropyl methylcellulose having binding properties, polyvinyl pyrollidone, methyl cellul se, gelatin, starch, sucrose, and lactose.

6. The controlled release tablet of claim 5 wherein the water soluble pharmaceutical binder comprises hydroxypropyl methylcellulose having binding properties.

7. The controlled release tablet of claim 5 wherein the water soluble pharmaceutical binder comprises polyvinyl pyrollidone.

8. The controlled release tablet of claim 6 wherein the hydroxypropyl methylcellulose having binding properties comprises hydroxypropyl methylcellulose having a nominal viscosity, 2 percent aqueous solution, of about 15 cps, a methoxy content of about 28–30 percent, a hydroxypropoxyl content of about 7–12 percent, and a particle size of 100% through a USS No. 30 mesh screen and 99% through a USS No. 40 mesh screen.

9. The controlled release tablet of claim 2 wherein the hydrophobic component comprises a wax-like insoluble material.

10. The controlled release tablet of claim 9 wherein the wax-like insoluble material is selected from the group consisting of hydrogenated vegetable oil and stearic acid:

11. The controlled release tablet of claim 10 wherein the wax-like insoluble material comprises a hydrogenated vegetable oil, the hydrogenated vegetable oil comprising a triglyceride of stearic acid.

12. The controlled release tablet of claim 2 further comprising up to about 5 percent by weight external lubricant.

13. The controlled release tablet of claim 12 wherein the external lubricant comprising glyceryl behenate.

14. The controlled release tablet of claim 13 wherein the external lubricant further comprises magnesium stearate.

15. The controlled release tablet of claim 2 wherein the hydroxypropyl methylcellulose with sustaining properties forms about 5–20 percent by weight of the tablet, the water soluble pharmaceutical binder forms about 2–8 percent by weight of the tablet, and the hydrophobic component forms about 5–15 percent by weight of the tablet.

16. The controlled release tablet of claim 3 wherein the percentage of niacin released in the 2 hours following following ingestion of the tablet is about 10–30 percent by weight.

17. The controlled release tablet of claim 3 wherein the percentage of the niacin released in the 8 hours following ingestion of the tablet is about 40–70 percent by weight.

18. The controlled release tablet of claim 17 wherein at least 90% release of the niacin occurs within 24 hours following ingestion of the tablet.

19. The controlled release tablet of claim 2 wherein the tablet is readily divisible into portions, each portion forming a smaller dose than the dose of the intact tablet.

20. The controlled release tablet of claim 3 wherein the tablet contains about 250 milligrams of niacin.

21. The controlled release tablet of claim 3 wherein the tablet contains about 500 milligrams of niacin.

22. The controlled release tablet of claim 3 wherein the tablet contains about 750 milligrams of niacin.

23. The controlled release tablet of claim 1 wherein the therapeutically active material forms from about 30–90% by weight of the tablet.

24. The controlled release tablet of claim 1 wherein the therapeutically active compound comprises niacin and forms from about 50–85 percent by weight of the tablet.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,126,145

DATED : June 30, 1992

INVENTOR(S) : KENNETH L. EVENSTAD et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page: please insert:

--[73] Assignee: Upsher-Smith Laboratories, Inc., Minneapolis, Minnesota--

In col. 10, ln. 43, please delete the word "following" after the word "following" and before the word "ingestion".

Signed and Sealed this

Fourteenth Day of September, 1993

Bruce Lehman

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

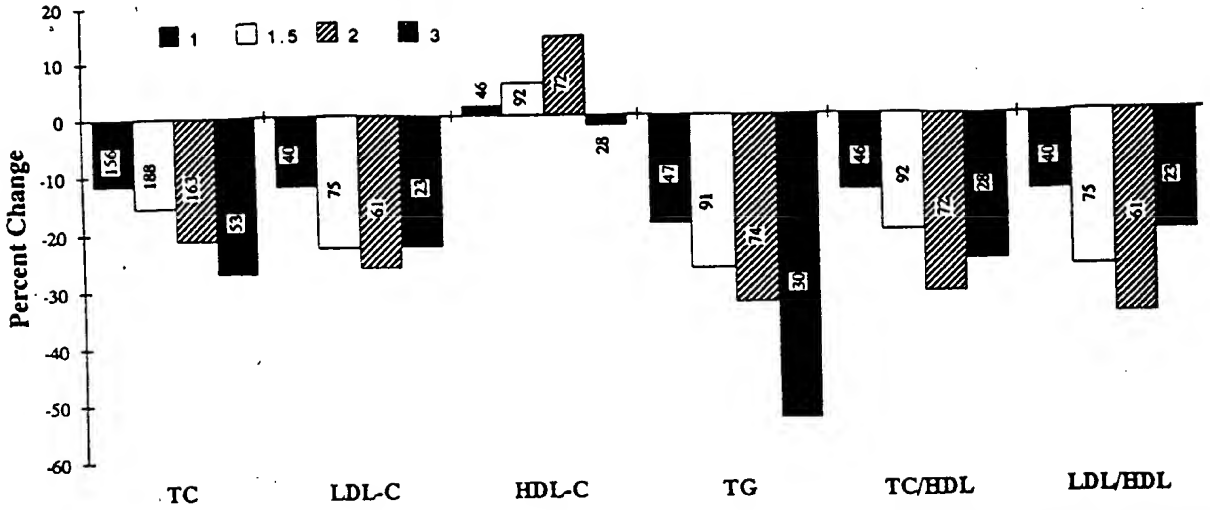

Figure 1. The relation between the controlled-release niacin dose and the plasma lipoprotein cholesterol response based on percentage change. HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; TC = total cholesterol; and TG = triglycerides.

controlled-release niacin or after dosage reduction. Twelve patients had vague abdominal and "flu-like" complaints that also resolved after discontinuation of controlled-release niacin. Two patients required hospitalization for niacin-induced hepatotoxicity. After dosage increases in controlled-release niacin (2.0 to 3.0 g/d and 3.0 to 6.0 g/d), both patients had marked increases in levels of hepatic enzymes, decreases in levels of serum albumin, anorexia, nausea, vomiting, and bilateral lower extremity edema that resolved after discontinuation of niacin.

The average daily dose of controlled-release niacin was greater in patients with probable niacin-induced hepatotoxicity compared with those with a rating of possible toxicity (3.1 g compared with 2.1 g, $P = 0.0075$). All patients with definite, probable, or possible hepatotoxicity associated with controlled-release niacin were included in the bivariate analysis of factors associated with increased risk (Table 4). Niacin-induced hepatic dysfunction was not associated with patient age or with diet or insulin-managed diabetes. Patients with hepatic dysfunction included 41 men and 1 woman equally distributed according to race. Factors associated with an increased risk for hepatotoxicity induced by controlled-release niacin included diabetes with receipt of oral hypoglycemic agents, preexisting liver disease, excessive alcohol use, and a higher mean daily dose of niacin. Three of the 4 patients with preexisting liver disease had a history of alcoholic hepatitis and the fourth patient had a history of granulomatous hepatitis. One patient with a history of alcoholic hepatitis also had a history of hepatitis B (currently negative for hepatitis surface antigen). One half (21 of 42) of the patients had at least one risk factor for the development of hepatic dysfunction. In addition, hepatic dysfunction followed a reasonable temporal sequence with concurrent controlled-release niacin in 4 patients receiving phenytoin, 1 patient receiving carbamazepine, and 1 patient receiving amiodarone.

The number of months on a given dose of controlled-release niacin before the development of hepatotoxicity ranged from 1 to 28 months (7.7 months [6.3 months], mean [SD]), whereas the number of months to recovery was 2.8 months ([SD] 2.6 months; range, 1 to 12 months). Peak chemistry values showed a fourfold increase in levels of AST, ALT, and alkaline phosphatase, a decrease (1 g/dL) in levels of serum albumin, and a 43% decrease in levels of total cholesterol.

Table 3. Liver Function Values and Blood Chemistry Results at Baseline and during Treatment with Controlled-Release Niacin*

Variable†	Baseline	Final Maintenance	Mean Paired Difference (95% CI)	*P* Value‡
AST, *U/L*	22.9	29.5	+6.6 (+4.6 to +8.6)	0.0001
ALT, *U/L*	29.0	35.8	+6.8 (+4.2 to +9.4)	0.0001
GGT, *U/L*	37.0	50.0	+13.0 (+2.5 to +23.5)	0.015
AP, *U/L*	85.1	106.7	+21.6 (+12.3 to +30.9)	0.0001
Glucose, *mmol/L*	6.54	6.98	+0.44 (+0.23 to +0.65)	0.0001
Uric acid, *μmol/L*	404.9	399.0	−5.9 (−14.0 to +2.2)	0.15
Albumin, *g/L*	44.7	42.6	−2.1 (−1.7 to −2.5)	0.0001

* AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; and GGT = gamma-glutamyl aminotransferase.
† To convert AST, ALT, AP, and GGT to SI values (μkat/L), divide by 60.0. To convert albumin to g/dL, divide by 10. To convert uric acid to mg/dL, divide by 59.48.
‡ Paired *t*-test.

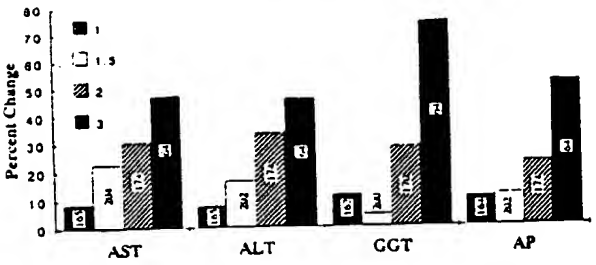

Figure 2. The relation between the controlled-release niacin dose and the percentage change in levels of liver enzymes. AP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; and GGT = gamma-glutamyl transferase.

Discussion

Despite the retrospective design of our study, the blood lipid–lowering effect of controlled-release niacin is clear. This benefit was apparent despite an environment in which optimal compliance with diet and drug therapy could not be verified. The dose-response relation for controlled-release niacin was evident up to a dose of 2.0 g/d for all lipid values. The failure to show further decreases in levels of LDL cholesterol and increases in HDL cholesterol with dosages of 3.0 g/d may result from small sample sizes (n = 23 and 28, respectively) and poor compliance because of the decreased patient tolerance seen at higher doses. The mean decrease in levels of LDL cholesterol seen at 1.5 g/d (−23%) compares favorably with that reported by Keenan and colleagues (17) (−20%) and McKenney and colleagues (15) (−22%) using different formulations of sustained-release niacin at 1.5 g/d. This decrease in levels of LDL cholesterol is greater than that reported by Knopp and colleagues (6) (−13%) using 3.0 g/d of time-released niacin capsules. This may be explained by poor patient tolerance and compliance (68% adherence) with time-released niacin and a lower bioavailability seen with time-released niacin (21). The decrease in levels of LDL cholesterol seen at 1.5 g/d with controlled-release niacin (−23%) is similar to that seen with 3.0 g/d of unmodified niacin (6) (−21%), suggesting that controlled-release niacin is twice as potent as crystalline niacin in decreasing levels of LDL cholesterol. In a subset of 160 patients, we found greater decreases in levels of LDL cholesterol occurring in patients with phenotype IIa compared with those with phenotype IIb (−25.4% compared with −15.1%). Further investigation is needed to characterize the effects of niacin in decreasing LDL cholesterol levels in different lipoprotein phenotypes.

The increases in HDL cholesterol levels with controlled-release niacin peaked at a dosage of 2.0 g/d (+14%). Keenan and colleagues (17) also reported a plateau effect with wax-matrix niacin at a dosage of 1.5 g/d (+9%). The reported effects of various sustained-release dosage forms of niacin given at low doses (1.0 to 2.0 g/d) on HDL cholesterol levels are quite variable (15, 17, 22–24) (+9% to +41%) and are similar to those reported by Knopp and colleagues (6) (+26%) in patients taking 3.0 g/d of unmodified niacin. We found a greater increase in levels of HDL cholesterol in those patients with lower baseline HDL levels (≤1.03 mmol/L [40 mg/dL], +12.2%; >1.03 mmol/L [40 mg/dL], +3.2%). This finding supports those reported by Lavie and colleagues (24) and Squires and colleagues (23) of marked improvement of HDL cholesterol levels in patients with very low (0.67 mmol/L [26 mg/dL] and 0.88 mmol/L [34 mg/dL], respectively) baseline HDL cholesterol levels (+30%, mean dose, 2.4 g/d; and +18%, mean dose, 1.3 g/d, respectively). Lavie and colleagues (24) also noted that patients with hypertriglyceridemia (3.50 mmol/L [310 mg/dL]) had greater increases in HDL cholesterol levels compared with those patients with normal triglyceride levels (1.84 mmol/L [163 mg/dL]) at baseline (+41% and +27%, respectively). These results suggest that the effect of niacin on HDL cholesterol levels requires further evaluation and may be affected by different dosage forms of niacin, baseline HDL cholesterol levels, baseline triglyceride levels, and other factors.

Triglyceride levels decreased progressively as the controlled-release niacin dosage increased from 1.0 and 3.0 g/d (Figure 2). The greater triglyceride-lowering effects we found with controlled-release niacin (1.5 g/d, −27%) relative to those found by Keenan and colleagues (17) with wax-matrix niacin (1.5 g/d, −9%) may be caused by the fact that baseline triglyceride levels were much higher in our sample of patients (3.48 mmol/L [308 mg/dL] compared with 1.63 mmol/L [144 mg/dL]). The triglyceride-lowering effects of 1.5 g/d of controlled-release niacin were identical (−27%) to those reported by Knopp and colleagues (6) for 3.0 g/d of unmodified niacin, again suggesting that controlled-release niacin is more potent than regular niacin.

Because our study was not controlled, many patients with relative contraindications to niacin therapy were not excluded. This allowed us to follow a large number of patients with diabetes mellitus (n = 160). Controlled-release niacin was poorly tolerated by patients with diabetes, with two thirds of them discontinuing therapy, in 40% of cases because of poor glycemic control. Henkin and colleagues (25) also found a greater discontinuation rate of niacin in patients with diabetes (88%) compared with patients without diabetes (33%). Garg and Grundy (26) found a deterioration of glycemic control with niacin therapy in patients with non-insulin–dependent diabetes mellitus and suggested that those with diabetes that was previously well controlled by diet may require oral hypoglycemic agents. This is consistent with our findings. Ten

Table 4. Risk-Factor Assessment of Niacin-associated Hepatic Dysfunction*

Variable	Hepatic Dysfunction		P Value
	Yes	No	
Patients, n	42	854	
Age, y*	59.9 ± 1.6	61.8 ± 0.3	
Final maintenance dose, g/d	2.33 ± 0.15	1.64 ± 0.03	0.001†
Diabetes mellitus, n(%)			
Diet or insulin	4 (9.5)	89 (10.4)	
Oral hypoglycemic agents	9 (21.4)	58 (6.8)	<0.0005‡
Liver disease by history, n (%)	4 (9.5)	18 (2.1)	<0.0005‡
Excessive alcohol use, n (%)	13 (40.6)§	100 (17.2)‖	<0.0005‡

* Values are mean ± SE.
† Unpaired t-test.
‡ Chi-square.
§ n = 32.
‖ n = 580.

patients whose diabetes was controlled by diet alone required oral hypoglycemic agents while receiving controlled-release niacin. A recommendation that patients with diet-controlled diabetes take oral hypoglycemic agents after poor glycemic control resulting from niacin therapy appears unwise given the increased potential for hepatic dysfunction that was observed in our study. Prolonged administration of niacin results in insulin resistance (27). The mean increase in glucose (+7%; average dose, 1.7 g/d) was similar to that found with 3.0 g/d (+7%) with unmodified niacin (28). Although no substantial biochemical changes in uric acid were noted, small increases in uric acid have been reported for unmodified niacin (28) and sustained-release niacin (23).

Niacin has been associated with increases in levels of hepatic enzymes. We found that controlled-release niacin resulted in a dose-related increase in liver enzymes over a dosage range of 1.0 to 3.0 g/d. Keenan and colleagues (17) and McKenney and colleagues (15) also found dose-related increases in levels of hepatic enzymes with different formulations of sustained-release niacin. Increases in levels of hepatic enzymes after patients received 1.0 g/d of controlled-release niacin were similar to those found with 3.0 g/d of unmodified niacin (28) (AST, +9% compared with +12% and alkaline phosphatase, +10% compared with +10%, respectively). A new finding was a small but statistically significant decrease in serum albumin levels, which correlated with a decrease in total cholesterol levels ($r = +0.31$) and may indicate a slight decrease in hepatic function.

Studies of the incidence of niacin-induced hepatotoxicity have found a variance of 0 to 46% in the incidence of increased levels of hepatic enzymes (29). The difficulty in determining the prevalence of niacin-induced hepatitis is due to differences in defining hepatotoxicity (increases in levels of enzymes, clinical disease, biopsy results, etc.), failing to establish a causal relation, differences in samples of patients studied, and differences in duration of the trial period. Our findings of a 2.2% prevalence of probable niacin-induced hepatotoxicity are similar to those reported by Blankenhorn and colleagues (4) (3.2%) in patients treated with crystalline niacin, 3 to 12 g/d.

Several recent case reports (9–14) describe hepatotoxicity associated with various sustained-release preparations of niacin. Etchason and colleagues (14) described increases in levels of hepatic enzymes in five patients treated with 3.0 g/d or less of sustained-release niacin. We also found that niacin-associated hepatic dysfunction occurs at relatively low doses (mean, 2.3 g/d). This is in contrast to hepatic dysfunction associated with higher doses of crystalline niacin. In addition, reports describe new-onset hepatotoxicity in patients switched from regular niacin to sustained-release niacin (11, 13, 14). McKenney and colleagues (15) reported a high incidence of hepatotoxicity (12 of 23, 52%) defined as an increase in levels of liver aminotransferases to more than three times the upper limit of normal, occurring with a different sustained-release dosage form of niacin. Five patients had symptoms of hepatic dysfunction that occurred at dosage levels of 2.0 to 3.0 g/d. Decreases in levels of LDL cholesterol were similar when comparing 1.5 g/d of sustained-release niacin (−21.9%) with 3.0 g/d of immediate-release niacin (−21.7%). This is consistent with our findings that hepatic dysfunction and decreases in levels of LDL cholesterol are associated with lower doses of sustained-release niacin when compared with unmodified niacin, suggesting potency differences. "Generalization" (30) of the reported results (15) to other dosage forms of immediate- or sustained-release niacin cannot confidently be made without pharmacokinetic and quality-control data or comparative clinical trials.

All niacin products available without prescription, regardless of formulation, are sold as nutritional supplements. Regulatory requirements for nutritional supplements, or foods, are less rigorous than those for prescription drug products. Differences in quality control and product variability may occur with different over-the-counter niacin products because some companies follow good manufacturing practices for prescription drugs for their nutritional supplement niacin formulation, whereas others do not.

Prescribing guidelines for niacin state that hepatic dysfunction is an absolute contraindication to its use and a history of liver disease is a relative contraindication. We found an increased risk for hepatotoxicity associated with preexisting liver disease, even though levels of hepatic enzymes were within normal limits at baseline. No data are available defining what factors may predispose patients to niacin-induced hepatic injury. We found support for a dose-response relation in that patients receiving a higher mean daily dose (2.3 g/d) of controlled-release niacin were more likely to develop hepatotoxicity than those receiving a lower mean daily dose (1.6 g/d). Those patients with excessive alcohol intake (medical record notation) have a greater propensity for developing hepatotoxicity while receiving niacin. Finally, niacin-induced hepatotoxicity was more prevalent in patients with diabetes who were receiving oral hypoglycemic agents. Thus, the risk for niacin-induced hepatitis may be greater in those patients taking agents also known to cause hepatic dysfunction, such as ethanol and sulfonylurea agents.

Controlled-release niacin appears to be more potent than immediate-release niacin with respect to efficacy and biochemical changes. The toxicity of controlled-release niacin is similar to that of immediate-release niacin if used in equipotent doses. Controlled-release niacin should be avoided in patients with hepatic dysfunction or a history of liver disease, patients with diabetes mellitus, and patients who use alcohol in excess. A safe level of alcohol intake in patients taking controlled-release niacin cannot be determined from our data. Most patients respond to a dosage range of 1.0 to 2.0 g/d. The incidence of flushing and itching can be minimized by titrating controlled-release niacin to an initial target of 1.0 g/d, prescribing it with meals, and pretreating patients with aspirin as necessary. Doses higher than 2.0 g/d are more likely to cause hepatotoxicity and require more frequent monitoring. Dosage increments should not be greater than 0.5 g/d, with levels of hepatic enzymes and blood glucose evaluated at baseline, within 6 weeks of any dose increase, and every 3 months while patients receive long-term therapy. Sustained-release formulations of niacin are not the same (21, 31) and should not be interchanged. Patients should be cautioned never to switch niacin formulations unless advised by their physicians. If patients are switched from immediate-release niacin to controlled-release niacin, a dose reduction of 50% to 70% is indicated.

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Promotion of extended-release niacin tablets at a Veterans Affairs medical center

FAYE F WU AND DAVID R GRAY

Abstract: A program to modify the prescribing of antilipemic agents by promoting the use of extended-release niacin tablets is described

Between December 1987 and August 1988, pharmacists at a 1188-bed Veterans Affairs medical center observed a large increase in the number of outpatient prescriptions for antilipemic agents In an attempt to control costs, a program to promote the use of extended-release niacin tablets for treating hyperlipemia was conducted during August and September 1988 Various educational materials on niacin were distributed to physicians A display on therapy of hyperlipemia was featured at the monthly drug fair, and articles on niacin were presented during a journal club meeting of ambulatory-care clinicians Pharmacists succeeded in having extended-release niacin tablets placed on the formulary in September Data on the number of prescriptions filled for antilipemic agents were collected before and after the niacin promotional program.

The number of prescriptions filled for extended-release niacin 500-mg tablets increased steadily during a six-month study period after the program ended, the number of prescriptions filled for regular niacin decreased by 50% As prescribing of extended-release niacin increased, prescribing of colestipol, gemfibrozil, and probucol declined The promotional program was well received by most of the medical staff.

A program of education and formulary management successfully changed physician prescribing habits for antilipemic agents

Index terms: Antilipemic agents; Colestipol; Drug use; Gemfibrozil; Niacin; Pharmacy, institutional, hospital; Prescribing; Probucol; Sustained-action medications
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Elevated serum low-density-lipoprotein (LDL) cholesterol has been established as an independent risk factor in the development of coronary artery disease [1-4] The growing concern of clinicians and the public over high serum cholesterol concentrations has led to the widespread use of antilipemic agents when dietary therapy alone is inadequate.

Niacin (nicotinic acid), which has been in use as an antilipemic agent since 1955, is very effective in lowering total cholesterol, LDL cholesterol, very-low-density-lipoprotein (VLDL) cholesterol, and triglycerides while simultaneously raising high-density-lipoprotein cholesterol [5-8] Niacin lowers cholesterol by inhibiting lipolysis, reducing LDL and VLDL synthesis, and increasing lipoprotein lipase activity to reduce triglycerides [7] In the Coronary Drug Project, niacin reduced the incidence of recurrent nonfatal myocardial infarction in men [9] Moreover, nine years after the end of the trial, niacin was associated with an overall reduction in mortality compared with placebo. Niacin in combination with colestipol can result in the regression of old atherosclerotic heart lesions and can prevent the occurrence of new ones [8] While many clinicians have recognized niacin as the drug of choice for certain types of hyperlipemic disorders, the common adverse effects (flushing and gastrointestinal distress) have limited patient acceptance of niacin [10]

Our facility is a 1188-bed Department of Veterans Affairs medical center that provides comprehensive medical and surgical services and acts as the principal teaching hospital for the college of medicine at the University of California at Irvine. Pharmaceutical services are provided by 71 pharmacists and 50 supportive personnel The inpatient pharmacy department provides unit dose and i.v. admixture services 24 hours a day, seven days a week Unit dose distribution is based on the decentralized pharmacy cart system Comprehensive outpatient services are provided; some 3000 prescriptions are filled daily Specialized clinical services, including drug information, pharmacokinetic monitoring, oncology, cardiology, antimicrobial management, home health care, anticoagulation management, and other direct patient-care activities, are provided by seven clinical pharmacy specialists and four clinical pharmacy residents.

We recently observed an increase in the use of costly antilipemic agents In about nine months (December 1987 to August 1988), the number of outpatient prescriptions for antilipemic medications rose from 171 to 326 per month In August 1988, colestipol was the most frequently prescribed antilipemic agent (45.7%), followed by niacin (26%), gemfibrozil (12%), probucol (5% or less), and lovastatin (5% or less)

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EXHIBIT #9

Niacin is the least costly of all the antilipemic agents. Extended-release niacin (Slo-Niacin; Upsher-Smith), although more costly than regular niacin tablets, is also much less expensive than the other cholesterol-lowering agents.

In an attempt to contain our antilipemic budget, we instituted a program to promote the use of extended-release niacin tablets as the drug of choice for treating hyperlipemia. The program included educational outreach and formulary management, which are known to be effective in changing prescribing patterns.[11-13] We describe the program here and report the effects it had on the prescribing of antilipemic agents.

Methods

Description of the Program. The program to promote the use of extended-release niacin tablets was conducted during a six-week period in August and September 1988. In August a newsletter supplement called "The Proper Use of Niacin for Hyperlipidemia," a titration guideline on niacin, a patient information handout, and a chart comparing costs of antilipemic agents were prepared and distributed to all physicians in our facility and to areas of the hospital where antilipemic agents are widely prescribed. In early September, extended-release niacin tablets were promoted through counterdetailing of physicians during our monthly drug fair. Pharmaceutical companies display their drug products in an open forum at the drug fair. A display to promote rational drug and dietary therapy of hyperlipemia was created by the clinical pharmacy resident and a clinical dietitian. Clinical pharmacists and residents at a booth answered questions on the management of hyperlipemia through diet, exercise, and medication. In mid-September, the clinical pharmacy resident presented key articles on niacin during a journal club meeting of ambulatory-care clinicians. At about this time, extended-release niacin (Slo-Niacin) was approved by the pharmacy and therapeutics committee for placement on the formulary; this approval was secured as a result of the joint efforts of the clinical pharmacy resident, the clinical pharmacy coordinator, and the director of the cholesterol clinic.

The primary focus of our educational efforts was the ambulatory-care physicians and the physicians assigned to the cholesterol clinic. The proper use of niacin was re-emphasized through written and oral methods. According to our recommended titration schedule, extended-release niacin should be slowly increased over a six-week period to a therapeutic dose of 1.5 g/day. Patients are given 250 mg twice daily for the first two weeks, 500 mg twice daily for the second two weeks, and 750 mg twice daily thereafter until the next scheduled appointment.

All educational materials used in the promotional program were prepared by the clinical pharmacy resident under the direction of her supervisor. It took about 10 days to prepare the written materials. Costs were minimal because the resident prepared and printed the materials using available desk-top publishing equipment.

Collection of Data. Outpatient prescription data were collected from patient records on a monthly basis for each antilipemic agent prescribed at our facility. Data were collected during an eight-month baseline period before the niacin promotion program began and a six-month study period after the program ended. The total number of prescriptions filled for each antilipemic agent was obtained for each period.

Results

Extended-release niacin (500- and 750-mg scored tablets) was added to our formulary in late September 1988. Slo-Niacin was selected over other extended-release products on the basis of cost and available dosage forms. The number of prescriptions filled for extended-release niacin 500-mg tablets increased steadily during the study period (Figure 1). While regular niacin 50- and 500-mg tablets remained on our formulary, the total number of prescriptions filled for regular niacin decreased by approximately 50% during the study period.

Figure 2 shows the percent distribution of prescriptions filled for niacin, colestipol, gemfibrozil, and probucol during the baseline and study periods. After completion of the promotional program in September 1988, prescribing of extended-release niacin tablets increased dramatically and prescribing of colestipol, gemfibrozil, and probucol declined. The total number of prescriptions filled for antilipemics increased from 326 per month at the time of the promotional program to 480 at the end of the study period.

Discussion

Many pharmacy departments have attempted to control drug costs by changing prescribing patterns. Techniques include formulary management, selection of therapeutic alternatives, use of specialized order forms, and education of prescribers.[11-14] The results show that our program to change the prescribing patterns for antilipemic drugs by promoting an effective and cost-efficient alternative, extended-release niacin tablets, was successful. The promotional program was well received by most of the medical staff. Approximately 60% of the medical staff visited our drug fair display booth. At the journal club presentation, 80% of the ambulatory-care staff physicians attended, and half of them participated in the discussion.

A few ambulatory-care physicians were somewhat resistant because of past patient complaints related to niacin-induced flushing. However, some of these physicians altered their antilipemic prescribing after they were informed about ways to minimize the ad-

Figure 1. Number of prescriptions filled for regular niacin 50 mg (A) and 500 mg (B) and extended-release niacin 500 mg (C) and 750 mg (D) during the six-month study period after the extended-release niacin promotion program

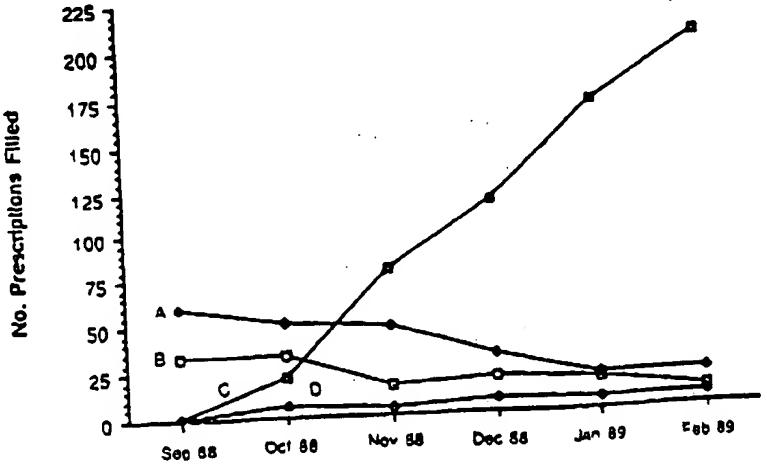
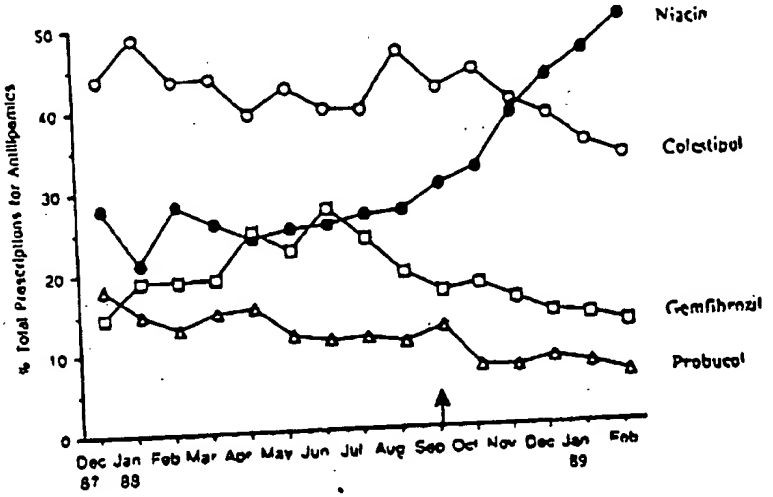


Figure 2. Percent distribution of prescriptions filled for individual antilipemic agents. The arrow indicates the end of the extended-release niacin promotion program



verse effects associated with niacin. Enhanced physician acceptance, as well as patient acceptance, contributed to our success.

Conclusion

A program of education and formulary management successfully altered physician prescribing habits for antilipemic agents, mainly by increasing the prescribing of extended-release niacin tablets.

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Loss of carbamazepine suspension through nasogastric feeding tubes

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Abstract: The apparent loss of carbamazepine suspension during administration through polyvinyl chloride nasogastric feeding tubes in vitro was studied.

Twelve methods of administering carbamazepine suspension (100 mg/5 mL) were tested; the methods differed with respect to nasogastric tube size, presence and type of diluent, and type of flush solution. Undiluted or 50% diluted carbamazepine suspension 200 mg was drawn up in a syringe and forced through adult or pediatric nasogastric feeding tubes. The tubes were immediately flushed twice with 50 mL of sterile water, 0.9% sodium chloride solution, or 5% dextrose solution, by using the same syringe used to administer the suspension. Samples were collected and analyzed for carbamazepine concentration by high-performance liquid chromatography. Each administration method was tested six times, and the results were subjected to analysis of variance.

Significant loss of carbamazepine was noted for four of the six methods in which undiluted suspension was administered. In these methods, adult and pediatric tubes were flushed with sterile water or 0.9% sodium chloride. No significant loss of drug occurred for any of the methods involving the use of diluent. Significant losses were associated with diluent and flush solution but not nasogastric tube size.

Carbamazepine suspension should be mixed with an equal volume of diluent before being administered through nasogastric feeding tubes.

Index terms: Anticonvulsants; Carbamazepine; Concentration; Dextrose; Diluents; Incompatibilities; Polyvinyl chloride; Sodium chloride; Water

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Carbamazepine is the drug of choice in the treatment of partial and generalized tonic-clonic seizures because of a relative absence of dysmorphic adverse effects and a low incidence of cognitive impairment when therapeutic concentrations in plasma are maintained.[1] One primary disadvantage of carbamazepine in the clinical setting is the limited number of dosage forms available. Until recently, carbamazepine was available commercially only in 200-mg oral tablets or 100-mg chewable tablets. In January 1988, carbamazepine suspension became commercially available.

The administration of drugs through nasogastric feeding tubes is common in the intensive-care setting. Data obtained in vitro suggest that binding interactions may occur between some drugs and plastics, resulting in decreased delivery of drug to the patient.[2-5] Most of these studies have focused on intravenously administered drugs, such as insulin and diazepam. With regard to potential binding to nasogastric tubes, only phenytoin has been studied. Recovery of phenytoin suspension has been studied after administration through percutaneous endoscopic gastros-

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EXHIBIT #10

A Comparison of the Efficacy and Toxic Effects of Sustained- vs Immediate-Release Niacin in Hypercholesterolemic Patients

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Objective.—To compare escalating doses of immediate-release (IR) and sustained-release (SR) niacin for effectiveness in reducing levels of low-density lipoprotein cholesterol and triglycerides and increasing levels of high-density lipoprotein cholesterol, and for the occurrence of adverse reactions, especially hepatotoxicity.

Design.—Randomized, double-blind, parallel comparison of IR and SR niacin administered sequentially at 500, 1000, 1500, 2000, and 3000 mg/d, each for 6 weeks.

Setting.—Cholesterol research center.

Patients.—Forty-six adults, 23 in each group, with low-density lipoprotein cholesterol levels greater than 4.14 mmol/L (160 mg/dL) after 1 month of a step 1 National Cholesterol Education Program diet.

Outcome Measures.—Fourteen-hour fasting lipid and lipoprotein cholesterol levels, results of clinical laboratory tests, a symptom questionnaire, and withdrawal rates.

Results.—The SR niacin lowered low-density lipoprotein cholesterol levels significantly more than IR niacin did at the dosage of 1500 mg/d and above, while IR niacin increased high-density lipoprotein cholesterol levels significantly more than SR niacin did at all dosage levels. The reduction in triglyceride levels was similar with IR and SR niacin. Nine (39%) of the 23 patients assigned to the IR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen (78%) of the 23 patients assigned to the SR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatoxic effects, while 12 (52%) of the 23 patients taking SR niacin did.

Conclusion.—The SR form of niacin is hepatotoxic and should be restricted from use. The IR niacin is preferred for the management of hypercholesterolemia but can also cause significant adverse effects and should be given only to patients who can be carefully monitored by experienced health professionals.

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ACCORDING TO the National Cholesterol Education Program, nicotinic acid is one of the primary drugs for treating hypercholesterolemia.[1] In daily doses of 2 to 3 g, it reduces total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels an average of 20% to 30%, lowers triglyceride levels 35% to 55%, and increases high-density lipoprotein cholesterol (HDL-C) levels 20% to 35%.[2-5] It also reduces levels of small, dense LDL-C and Lp(a) lipoprotein, both of which are associated with increased risk of coronary heart disease (CHD).[6,7] It is effective in the treatment of hypercholesterolemia, as well as mixed hyperlipidemia and hypoalphalipoproteinemia.[8-10] It has been shown to reduce total and CHD mortality when used in primary prevention[11] and to slow or reverse the progression of atherosclerosis when used with bile acid resins in secondary prevention.[11-15] It is widely available as an over-the-counter product and is one of the least expensive drugs for the management of dyslipidemia.

For editorial comment, see p 709.

Despite these numerous advantages, nicotinic acid has several notable disadvantages, mostly relating to its toxic effects. It is generally not well tolerated by patients, causing vasodilatory side effects in up to 100% of patients, particularly when administered in an immediate-release (IR) dosage form.[2,3] In clinical trials, about 25% of patients have to discontinue niacin use because of these symptoms.[3,16,17] Sustained-release (SR) dosage forms of nicotinic acid have been recommended to reduce vasodilatory side effects. Unfortunately, they are more likely to produce gastrointestinal tract side effects and may be less effective in lowering LDL-C levels and increasing HDL-C levels.[2,3] More importantly, there have been numerous case reports of hepatotoxic effects associated with SR niacin.[18-31]

This study was conducted to compare SR and IR niacin directly in a well-designed clinical trial. The objective was to compare escalating doses of IR and SR niacin for efficacy in reducing LDL-C and triglyceride levels and increasing HDL-C levels and for the occurrence of adverse effects as reflected by bothersome symptoms, changes in results of laboratory tests for blood glucose or liver function, and withdrawals from the study.

PATIENTS AND METHODS

Patient Selection

The study protocol was approved by the institutional review board, and a consent form was signed by each patient.

From the Schools of Pharmacy (Dr McKenney) and Medicine (Dr Proctor), Medical College of Virginia, Virginia Commonwealth University, Richmond; Baptist Medical Center, Little Rock, Ark (Dr Harris); and College of Medicine, Pennsylvania State University, Hershey (Dr Chinchili).

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Adults with a history of high blood cholesterol levels were recruited by means of advertisements in the local newspaper and were taught the National Cholesterol Education Program saturated fat- and cholesterol-restricted step 1 diet by a registered dietitian.[1] Those who had LDL-C levels greater than 4.14 mmol/L (160 mg/dL) after following this diet for at least 1 month were eligible for the study. Patients were excluded if they had major medical problems; familial lipid disorders; secondary causes of hypercholesterolemia, including hypothyroidism, obesity (>140% of ideal body weight), diabetes mellitus, and renal disease; abnormal liver function; triglyceride levels greater than 9.05 mmol/L; or contraindications to niacin therapy, including active peptic ulcer disease; or if they were receiving drugs that could alter cholesterol levels. Patients whose conditions were stable with a fixed dose of antihypertensive or thyroid replacement medication, or conjugated estrogens for longer than 6 months, could participate if they maintained the same dose throughout the study. Patients were required to discontinue other cholesterol-lowering drug therapy 4 weeks before beginning the diet lead-in phase.

Study Design

This was a randomized, double-blind, parallel-group study. It lasted 36 weeks and consisted of a 6-week lead-in period followed by five 6-week treatment periods. During the lead-in period, a medical history was taken and clinical laboratory tests and a physical examination were performed. Compliance with the diet was established by evaluating the patient's diary of all foods consumed for 3 days with a food record rating (FRR) score, a scoring system that roughly quantifies the saturated fat content in the diet.[32] Patients who obtained an FRR score of -15 or less at the end of the lead-in period were judged to be following a National Cholesterol Education Program step 1 diet. This diet was continued throughout the study and monitored by the use of 3-day diet diaries and FRR scoring at the end of each treatment period.

Patients were randomly assigned to receive IR niacin (Rugby Laboratories, West Hempstead, NY) or SR niacin (Goldline Laboratories, Ft Lauderdale, Fla). The drug was administered twice daily in identical-appearing capsules. During the first treatment period, patients took 250 mg/d for 1 week, followed by 500 mg/d for 5 weeks. Thereafter, the following dosages were sequentially introduced, and the patient took each one for 6 weeks: 1000, 1500, 2000, and 3000 mg/d. Dosages were escalated even if no increase was required for control of the patient's cholesterol level.

Table 1.—Mean Global Score and Percentage of Patients Who Reported at Least Moderately Bothersome Adverse Symptoms While Taking Escalating Doses of Immediate- or Sustained-Release Niacin

Niacin Daily Dose, mg	No. of Patients	Global Score	% of Patients		
			Vasodilatory Symptoms*	GI Tract Symptoms†	Fatigue
Immediate release					
Baseline	23	3.8	22	22	4
500	23	6.6‡	48	26	4
1000	19	6.7‡	53	26	11
1500	19	7.9‡	32	32	21
2000	18	8.1‡	39	39	22
3000	14	6.3‡	29	14	14
Sustained release					
Baseline	23	2.9	22	26	7
500	23	3.2	13	22	4
1000	23	5.1	22	13	17
1500	21	4.5	19	13	19
2000	18	4.7	17	17	11
3000	9	7.1‡	22	56	33

*Flushing, tingling, headache, warmth, itching.
†GI indicates gastrointestinal. Nausea, gas, heartburn, diarrhea.
‡$P<.01$ vs baseline.

All patients were taught how to recognize and ameliorate side effects and adjust doses. Patients were advised to take an adult aspirin tablet 30 minutes before the morning niacin dose and to take each dose with food to minimize adverse effects.

Study Measurements

Two 14-hour fasting blood samples for lipid and lipoprotein cholesterol measurements were obtained in all six study periods, one at the end of the fourth and another at the end of the sixth week. During the lead-in period, the average of these values was used to qualify patients for the study and to establish baseline levels. During each treatment period, the average of these values served as the measure of drug effect. If the patient was withdrawn from the study during any treatment period, any lipid values obtained were included in the efficacy analysis. Lipid results were available to the investigators throughout the study for use in encouraging patient compliance.

At the end of each study period, the occurrence of adverse effects was determined by use of patient history, clinical laboratory tests, and a symptom questionnaire. Patients were encouraged to report adverse effects at any time. If the adverse effect was clinically significant, the patient was withdrawn from the study. If it was not clinically significant, the patient was asked to reduce the niacin dosage to the previously tolerated dosage for 1 week and then to resume the scheduled dosage. If the adverse effect persisted or recurred, the patient was withdrawn from the study. Patients were always withdrawn when the results of liver function tests were greater than three times the upper limit of normal.

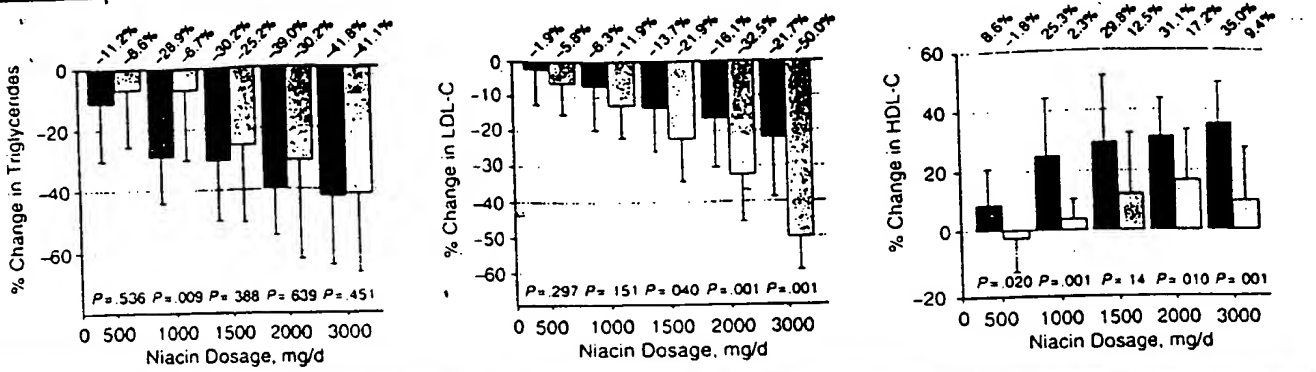
The symptom questionnaire contained a list of 11 symptoms commonly reported with niacin therapy (ie, vasodilatory symptoms of flushing, tingling, warm feeling, headache, rash, and itching; gastrointestinal tract symptoms of nausea, gas, heartburn, and diarrhea; and fatigue). For each symptom, patients were asked to indicate how bothersome the symptom had been during the previous 6 weeks. The patient's responses were converted to numeric scores by assigning 0 to 4 for least to most bothersome. A global score for each patient was determined at the end of each treatment period by adding the numeric scores of each symptom. The global score provided an estimate of the overall adverse effects associated with niacin therapy; it did not indicate that all adverse effects were of equal significance.

Compliance with niacin therapy was assessed by a capsule count at the end of each treatment period.

The laboratory used for this study was standardized by participation in the Centers for Disease Control Lipid Standardization Program. All analytes met Centers for Disease Control requirements for accuracy and precision.[33] Total cholesterol and triglyceride levels were measured enzymatically.[34] For the HDL-C determination, plasma was fractionated with 0.092-mol/L manganese chloride plus 183-U/L heparin solution followed by centrifugation, and the supernatant fraction was assayed for cholesterol.[35] The very-low-density lipoprotein cholesterol and LDL-C levels were calculated by the Friedewald formula applied to the measured values.[36]

Statistical Methods

The minimum sample size estimation at a power $(1-\beta)$ of 90% and $\alpha=.05$ for



Mean percentage change (with SD) in triglycerides (left), low-density lipoprotein cholesterol (LDL-C) (center), and high-density lipoprotein cholesterol (HDL-C) (right) levels with immediate-release (darker bars) and sustained-release (lighter bars) niacin as dosage was increased from 500 to 3000 mg/d. Baseline levels were as follows: triglyceride, 2.11±1.02 mmol/L in the immediate-release group and 1.96±0.84 mmol/L in the sustained-release group; LDL-C, 5.24±0.73 mmol/L (202.8±28.6 mg/dL) in the immediate-release group and 5.20±0.59 mmol/L (201.1±22.8 mg/dL) in the sustained-release group; and HDL-C, 1.15±0.32 mmol/L (44.3±12.2 mg/dL) in the immediate-release group and 1.28±9.49 mmol/L (49.6±15.6 mg/dL) in the sustained-release group. Baseline values for immediate-release and sustained-release niacin were not significantly different for triglycerides (P=.251) or LDL-C (P=.775) by t test. Baseline HDL-C values for immediate-release and sustained-release niacin were significantly different (P=.002) by t test. P values for cumulative changes in lipids and lipoproteins from baseline between immediate-release and sustained-release niacin are given in insert with each daily dosage (determined by repeated-measures analysis of variance).

a two-arm parallel study with two-tailed testing to detect a difference of 0.65 mmol/L (25 mg/dL) in LDL-C level with an SD of 0.67 mmol/L (26 mg/dL) was 23 for each group. The sample size required to determine a 0.23-mmol/L (9-mg/dL) difference in HDL-C level with an SD of 0.23 mmol/L (9 mg/dL) was 21 for each group.[36]

Efficacy analyses were performed by the Statistical Analysis System. A repeated-measures analysis of variance (ANOVA) was conducted for each of the following response variables: total cholesterol, triglyceride, LDL-C, very-low-density lipoprotein cholesterol, HDL-C, glucose, uric acid, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels; and global adverse symptom score. The treatment groups were unbalanced because of patient withdrawals; therefore, the restricted maximum likelihood estimation method described by Jennrich and Schluchter[37] was applied. The model consisted of terms for each patient's baseline mean and terms for mean changes from baseline for each period for each dosage form; the correlation structure within each patient was modeled as a general autoregressive process. From the results of the repeated-measures ANOVA, approximate t tests were constructed for comparing the dosage forms within each period. For the lipid and lipoprotein cholesterol variables, measurements were taken at the end of weeks 4 and 6 of each period, so preliminary repeated-measures ANOVAs were performed on the differences between the two measurements to determine whether it was legitimate to average the values from these 2 weeks. All the calculations for the repeated-measures ANOVAs were performed in PROC MIXED of SAS 6.07.

Pearson's partial correlations among the lipid and lipoprotein cholesterol responses and alanine and aspartate aminotransferase levels were calculated for each dosage form. Partial correlations were used to adjust for the repeated measurements over dosage level for each dosage form. Exact t tests were constructed to test that the partial correlations were significantly different from zero, and Fisher's z-transformation was applied to construct approximate 95% confidence intervals.[38] All such calculations were performed by the multivariate ANOVA statement in PROC GLM of SAS 6.07.

The period of a patient's last visit before withdrawal (last visit if the patient did not withdraw) was analyzed by means of ordinal logistic regression in which the regressor represented the difference between the two dosage forms. This was performed in PROC LOGISTIC of SAS 6.07. Also, the rate of withdrawals with the two dosage forms was compared by means of a likelihood-ratio χ^2 test.

RESULTS

Study Patients

Fifty patients met the inclusion criteria; four patients were subsequently withdrawn because they required medical procedures that disrupted niacin therapy or were not compliant with the protocol. The remaining 46 patients, including 24 men and 22 women, of whom 32 were white and 14 black, were enrolled into the study.

Of these 46 patients, 23 were randomized to each treatment group. The mean (±SD) ages of patients in the IR and SR groups were 55.0±10.8 years and 52.0±10.4 years, respectively. Approximately half of the patients in each group were female and 35% were black. Patients in each group had from zero to four risk factors for CHD; family history, male sex, hypertension, and smoking were the most prevalent risk factors present. None of the patients had a history of CHD. The mean (±SD) baseline weight for patients in the IR group was 80.6±15.0 kg, and for patients in the SR group, it was 81.4±10.5 kg. The mean baseline values for LDL cholesterol and triglycerides were similar (P=.851 and .251, respectively), but the mean baseline HDL-C levels were different (P=.002) (Figure).

Compliance with the National Cholesterol Education Program diet and niacin regimens was acceptable throughout the study. The mean baseline FRR score was 8.8 (range, 3 to 15) in both groups. Mean FRR scores ranged between 9.0 and 11.2 during treatment periods and were not different between the IR and SR niacin groups. Individual scores greater than 15 were encountered in only 14 (7%) of the 208 individual patient diaries analyzed, and these scores decreased to less than 15 on reinforcement counseling. Patients took an average of 92% to 98% of prescribed niacin doses during the study's five treatment periods. Capsule counts were not different during any treatment period. Only 10 (7%) of 140 individual patients took less than 80% of prescribed doses during any one treatment period; these patients returned to acceptable levels after counseling by the investigator.

Efficacy

Total cholesterol level was reduced by 1.5%, 4.8%, 9.8%, 11.1%, and 15.9% with IR niacin and by 5.6%, 9.0%, 17.0%, 24.7%, and 40.2% with SR niacin as dosages were

increased from 500 mg/d to 1000, 1500, 2000, and 3000 mg/d, respectively. Mean percentage changes in LDL-C, triglyceride, and HDL-C levels with escalating doses of IR and SR niacin are presented in the Figure. The reduction in triglyceride levels was similar with IR and SR niacin; a significant difference between the dosage forms was detected only at the dosage of 1000 mg/d.

The SR niacin lowered LDL-C levels significantly more than did IR niacin at dosages of 1500 mg/d and higher (Figure). The 1500-mg SR niacin dose and the 3000-mg IR niacin dose produced similar reductions in LDL-C levels (21.9% and 21.7%, respectively). At 1500 mg daily, SR niacin reduced LDL-C level in all 21 patients who received it (range, −3.1% to −50.0%), whereas IR reduced it in 17 of 19 patients (range, +13.3% to −40.2%). At 1500, 2000, and 3000 mg/d, IR niacin lowered LDL-C levels to less than 4.14 mmol/L (160 mg/dL), a common goal of therapy, in seven (39%) of 19 patients, nine (50%) of 18 patients, and nine (64%) of 14 patients, respectively. The use of SR niacin achieved this outcome in 12 (57%) of 21 patients, 14 (78%) of 18 patients, and nine (100%) of nine patients, respectively. For SR niacin, there was a significant correlation between the decrease in LDL-C level and the decrease in triglyceride level (r=.40, P=.001); the decrease in LDL-C and triglyceride levels with IR niacin was not significantly correlated (r=−.04, P=.772). Similar to the reduction in LDL-C level, total cholesterol levels decreased 2%, 5%, 10%, 11%, and 16% with IR niacin and 5%, 9%, 17%, 25%, and 39% with SR niacin as doses were increased.

The use of IR niacin increased HDL-C level significantly more than did SR niacin at all dosages (Figure). The increase with IR niacin was a substantial 25% at 1000 mg/d and 35% with 3000 mg/d. The dosage of 1000 mg/d of IR niacin increased HDL-C level in all 23 patients (range, 5.6% to 89%), while SR niacin increased it in only 15 of the 23 patients (range, −12.3% to 26.0%). The increase in HDL-C level was correlated with the reduction in triglyceride levels with both IR niacin (r=−.33, P=.008) and SR niacin (r=−.33, P=.007). The HDL-C levels were significantly lower at baseline in IR niacin–treated patients, which may have influenced these results.

Adverse Effects

Vasodilatory symptoms were reported to be at least moderately bothersome by approximately half of the patients taking IR niacin at dosages of 500 or 1000 mg/d; fewer reported these symptoms at higher dosages (Table 1). Flushing was the most frequently reported vasodilatory symptom. Patients taking SR niacin did not report an increase in vasodilatory symptoms over baseline levels. The frequency of gastrointestinal tract symptoms was increased only in patients taking 3000 mg/d of SR niacin. Fatigue was reported by patients in both the IR and SR niacin groups. Overall, global symptom scores were significantly greater than baseline for IR niacin at all dosages tested, but only at 3000 mg/d for SR niacin. The global scores for IR and SR niacin were not significantly different from each other at any dosage level.

Table 2.—Effect of Escalating Doses of Immediate- and Sustained-Release Niacin on Liver Function Tests*

Niacin Daily Dose, mg	Mean AST, U/L	Mean ALT, U/L	Mean Alkaline Phosphatase, U/L
Immediate Release			
0	22.2	22.7	95
500	21.3	21.5	97
1000	20.7	20.5	96
1500	21.4	20.7	98
2000	22.3	21.1	95
3000	24.3	22.4	101
Sustained release			
0	23.8	25.6	95
500	27.9	29.5	95
1000	40.4	36.3	106
1500	36.6†	39.0†	105
2000	56.5†	59.1†	136
3000	97.0†	100.0†	135

*AST indicates aspartate aminotransferase; ALT, alanine aminotransferase (usual reference interval for the study laboratory was 0 to 50 U/L for both).
†P<.05 vs baseline.

As dosages were escalated from 500 to 3000 mg/d, mean fasting glucose levels increased from a baseline of 5.4 mmol/L (98 mg/dL) to 5.6, 5.7, 5.9, 5.9, and 6.2 mmol/L (100, 103, 106, 106, and 112 mg/dL) with IR niacin and from 5.4 mmol/L (98 mg/dL) to 5.7, 5.6, 5.7, 6.2, and 7.5 mmol/L (102, 100, 102, 112, and 136 mg/dL) with SR niacin. Compared with baseline values, these increases were not significant with IR niacin; the increase with 2000 mg/d and above of SR niacin was significant (P=.009, ANOVA). By the end of the study, three patients in each group who were initially euglycemic had a fasting glucose level greater than 7.8 mmol/L (140 mg/dL). None of these patients experienced hyperglycemic symptoms, nor were they given glucose-lowering therapy. There was no appreciable change in mean uric acid levels with either the IR or SR niacin group as dosages were escalated, and no patients experienced gouty arthritis during the study. There was a substantial increase in mean liver aminotransferase and alkaline phosphatase levels in patients receiving SR niacin; these levels reached significance at 1500 mg/d and above (Table 2). There were no significant changes in liver function test results in patients receiving IR niacin.

Toxic effects severe enough to require withdrawal from therapy occurred in patients taking both dosage forms. With IR niacin, nine (39%) of the 23 patients had to be withdrawn before completing the dosage of 3000 mg/d (Table 3). The most common reasons for withdrawal from IR niacin were vasodilatory symptoms (ie, flushing, itching, rash), fatigue, and acanthosis nigricans. Withdrawals because of vasodilatory symptoms were encountered at dosages as low as 1000 mg/d, whereas acanthosis nigricans was encountered in two patients taking 2000 mg/d and one patient taking 3000 mg/d. The increase in fasting blood glucose level in patients who developed acanthosis nigricans was not different from the mean change for all patients.

The adverse effects that caused patients to withdraw from IR niacin therapy subsided completely in every case when therapy was discontinued. Recovery occurred within a few days for vasodilatory and fatigue symptoms to within several months for acanthosis nigricans. One patient who had been taking IR niacin was admitted to a local hospital 2 days after completing the study because of a bleeding peptic ulcer that required transfusion. The patient had mentioned no abdominal symptoms on his last study visit. He had a history of peptic ulcer disease but had been asymptomatic for the previous 7 years.

Eighteen (78%) of the 23 patients assigned to the SR dosage form had to be withdrawn before completing the dosage of 3000 mg/d (Table 3). Liver aminotransferase elevations more than three times the upper limit of normal were encountered in 12 of the 18 patients who were withdrawn; five of these 12 patients also had symptoms of hepatic dysfunction (ie, fatigue, nausea, anorexia). Withdrawals resulting from elevated liver aminotransferase levels

occurred at dosages as low as 1000 mg/d; symptoms of hepatic dysfunction were encountered only at the dosage levels of 2000 and 3000 mg/d. The LDL-C level in the 12 patients who withdrew because of liver function abnormalities decreased more than was expected with the dosage of niacin taken; the mean cumulative LDL-C level reduction achieved with the previous, tolerated dose was 22.7% compared with 40.5% with the "toxic" dose taken at the time of withdrawal from the study. All liver function abnormalities returned to normal within 4 weeks after niacin was discontinued.

By application of ordinal logistic regression to the period of a patient's last visit in the study before withdrawal, we did not discover a significant difference ($P=.214$) between the dosage forms for the timing of the withdrawals. However, by application of a likelihood-ratio χ^2 test, we discovered a significant difference ($P=.037$) between the dosage forms for the proportion of withdrawals.

Table 3.—Patients Withdrawing From Niacin Treatment With Escalating Daily Doses and Reasons for Their Withdrawal

	Immediate-Release Niacin		Sustained-Release Niacin	
Daily Dose, mg	No. of Patient Withdrawals	Reason of Withdrawal	No. of Patient Withdrawals	Reason for Withdrawal*
500	0	...	0	...
1000	4	Nausea, flushing; itching; flushing; fatigue, rash	2	Fatigue; elevated LFT results
1500	1	Rash	2	Elevated LFT results
2000	3	Fatigue, nausea; acanthosis nigricans (2 patients)	7	Fatigue, listlessness; elevated LFT results; elevated LFT results and fatigue; elevated LFT results and nausea (2 patients); nausea, rash, itching; diarrhea, weight loss
3000	1	Acanthosis nigricans	7	Elevated LFT results (3 patients); elevated LFT results and anorexia; itching; nausea; elevated LFT results, nausea, vomiting, fatigue
Total, No. (%)	9/23 (39)		18/23 (78)	

*LFT indicates liver function test.

COMMENT

Our study demonstrated that SR niacin reduced LDL-C levels more than IR niacin did. In concert with other controlled trials comparing IR and SR niacin, IR niacin reduced LDL-C levels 14% to 22% with dosages of 1500 to 3000 mg/d. However, SR niacin reduced LDL-C levels 22% to 50%, whereas other investigators only achieved a 13% to 25% reduction with dosages of 1500 to 3000 mg/d.[2,4] In the largest clinical study that used IR niacin, the Coronary Drug Project, 3000 mg/d reduced total cholesterol level an average of 10% in all patients receiving it and 16% in patients whose baseline total cholesterol level was greater than 7.24 mmol/L (280 mg/dL), which was similar to that achieved in patients enrolled in our study.[39]

It is not apparent why there was a difference in the LDL-C–lowering efficacy between IR and SR niacin in our study. Factors that could cause differences, including gender, race, age,[40] weight, baseline cholesterol levels, baseline triglyceride levels (which are suggestive of LDL subclass patterns[7]), and compliance, were equally distributed in the two study groups. The major difference between the groups was the prevalence of liver toxic effects associated with SR niacin, and this may have accounted for the greater LDL-C–lowering effect. Patients who experienced hepatic dysfunction with SR niacin had a greater LDL-C level reduction than was anticipated on the basis of the reduction with the previous, tolerated dose. Furthermore, nine of the 12 patients who developed hepatotoxic effects were taking the higher niacin dosages, 2000 and 3000 mg/d, suggesting a dose-related toxic effect.

Our study has also shown that IR niacin had a greater effect on increasing HDL-C levels than did SR niacin. A dosage of 1000 mg/d of IR niacin produced an impressive 25% increase in HDL-C level, whereas the greatest increase with SR niacin was only 17% with 2000 mg/d. Other controlled clinical trials have found that HDL-C level increased 14% to 37% with 1500 to 3000 mg/d of IR niacin but only 8% to 9% with similar doses of SR niacin.[2,4] Investigators using uncontrolled methods have reported increases of 25% to 41% in HDL-C level with dosages of 1000 to 3000 mg/d of SR niacin.[5,10,16]

The reason for the divergent effects of IR and SR niacin on HDL-C level is also unclear. One determinant of the efficacy in increasing HDL-C is the change in triglyceride level. A large increase in HDL-C level accompanies a large reduction in triglyceride levels[4,6,9,16] and vice versa.[6,17] This, however, does not explain the divergent effects we observed between IR and SR niacin. Both IR and SR niacin produced similar reductions in triglyceride levels, but SR niacin did not produce comparable increases in HDL-C level. This suggests that different mechanisms may be operative. It is possible that both drugs reduce the exchange of triglyceride and cholesterol ester between very-low-density lipoprotein and high-density lipoprotein particles, which results in higher HDL-C levels,[6] but that IR niacin has other effects that cause an even greater increase in HDL-C level. These mechanisms require further investigation.

One of the most important findings of our study was the extent of hepatotoxicity with SR niacin. This effect has been widely chronicled in recent years, primarily through patient case reports.[18-31] Practically all of the patients in these case reports were taking SR niacin, often after being switched from an IR to an SR dosage form.[41] None of the reports provides information on the cholesterol levels of the affected patients. In concert with our findings, most cases of hepatotoxicity have occurred in patients taking SR niacin dosages of 2000 mg/d or more. The duration of niacin therapy before hepatotoxicity is experienced has been as little as 1 week to as much as 48 months, suggesting that toxic reactions in our patients might have been even more frequent with a longer study.[41] As in our patients, symptoms accompanied some of the reported cases of elevated liver function tests; most commonly these symptoms included malaise, fatigue, somnolence, weakness, anorexia, nausea, vomiting, epigastric pain, and dark urine.[18-31] As in our patients, signs and symptoms of hepatotoxicity resolved completely within weeks of discontinuing niacin therapy. Several cases of severe liver dysfunction and fulminant hepatitis, however, have been reported, some progressing to stage 3 and 4 encephalopathy and one requiring liver transplantation.[19,24,28]

Our study is one of the few controlled trials to document a high prevalence of hepatotoxic effects with the SR compared with the IR dosage form. Hepatotoxic effects occurred in 52% of SR niacin–treated patients and 0% of IR niacin–treated patients. Christensen et al[2] and Henkin and Oberman[42] also found hepatotoxic effects in about half of their SR niacin–treated patients. Other investigators, however, have found few

cases of hepatotoxicity with SR niacin.[4,5,16,17] This suggests that there may be differences in the prevalence of this problem among the different SR niacin products. However, many different SR products with various release mechanisms, including Nicobid[20] from Rhone-Poulenc Rorer Pharmaceuticals Inc (Collegeville, Pa), Slo-Niacin[21] from Upsher-Smith (Minneapolis, Minn), Nature's Plus,[18] Niatrol,[22] Endur-Acin,[21] and generic products from Goldline[21] (used in this study), Rugby Laboratories, Rockville Center, NY,[23] and Major[21] Pharmaceutical, San Diego, have been implicated in niacin-induced hepatitis. It has also been suggested that hepatotoxic effects may be related to a contaminant introduced during the manufacture of the niacin product,[23] but there is no evidence to support this contention.

Our study results support a careful examination of the current over-the-counter availability of niacin in the United States. Only two products that have been approved by the Food and Drug Administration for use in the treatment of hypercholesterolemia are currently marketed, Niacor (Upsher-Smith) and Nicolar (Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville). All other IR dosage forms and all SR dosage forms are available as nonprescription drugs for the treatment of nicotinic acid deficiencies and are not regulated by the Food and Drug Administration. Given the degree of toxic effects we encountered, we believe that allowing niacin to remain on the nonprescription market, where it may be used in high doses for cholesterol lowering without proper monitoring by trained health professionals, presents a potentially serious public health problem.

We also believe that the safety of niacin deserves further evaluation, especially the potential for hepatic toxic effects with SR niacin. From the perspective of a research center that routinely evaluates the efficacy and safety of drug therapies for hypercholesterolemia, the incidence and severity of adverse reactions experienced with both niacin dosage forms in the present study, but particularly with SR niacin, were much greater than any investigational drug we have evaluated for hypercholesterolemia. If niacin were being evaluated for efficacy and safety and our experiences were replicated by others, we do not believe that it would be approved by the Food and Drug Administration for use in the management of hypercholesterolemia.

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Medical Sciences Bulletin

Medical Sciences Bulletin Contents

The Toxicity of Niacin

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Niacin (nicotinic acid) is widely used for reducing serum cholesterol levels, in part because it is effective, and in part because it is available and cheap. In doses of 2 to 3 g daily, it reduces levels of total and high-density lipoprotein cholesterol (LDL-C) by an average of 20% to 30%, reduces triglyceride levels 35% to 55%, increases high-density lipoprotein cholesterol (HDL-C) 20% to 35%, and reduces Lp(a) lipoprotein. In primary prevention, niacin reduces total mortality as well as mortality from coronary artery disease; used in secondary prevention along with bile acid resins, it slows or reverses the progression of atherosclerosis. And it costs only about $2.00 for a 10-day supply. Does all this sound too good to be true? Results from a recent study by McKenney et al. (Medical College of Virginia School of Pharmacy) indicate that not all the news about niacin is good news. In therapeutic doses, niacin can be dangerous, particularly sustained-release niacin.

The Virginia researchers conducted a randomized, double-blind, parallel-group comparison of sustained-release (SR) and immediate-release (IR) niacin in 46 patients with hypercholesterolemia. The 36-week trial included a 6-week evaluation and instruction period followed by five 6-week treatment periods during which niacin was given in escalating doses (500 mg/day initially, increasing up to 3Êg/day). Both the IR niacin product (**Rugby Laboratories**, division of Marion Merrell Dow) and the SR niacin (**Goldline Laboratories**) were effective for improving the lipid profile. At the highest (3-g) dose, SR niacin reduced total cholesterol by about 40% and LDL-C by 50%, while IR niacin reduced total cholesterol by about 16% and LDL- C by about 22%. Both formulations at the 3-g dose reduced triglycerides by about 41%. IR niacin elevated HDL-C by 35% at the 3-g dose, while SR niacin elevated HDL-C by only 9.4%, a significant difference.

Both formulations were associated with considerable side effects. Nine of the 23 patients assigned to IR niacin withdrew from the trial before completing the 3-g dose phase because of adverse reactions, including vasodilation (flushing, itching, rash), fatigue, and acanthosis nigricans (a wart-like skin eruption). Eighteen of the 23 patients in the SR niacin group withdrew before completing the 3-g dose phase because of gastrointestinal effects, fatigue, and hepatotoxicity. Thus, 39% of patients on IR niacin and 78% of those on SR niacin withdrew because of side effects.

More than half the patients in the SR niacin group showed evidence of hepatotoxicity. Liver aminotransferase levels were three times the upper limit in 12 of the 18 who withdrew, and 3 patients had symptoms of hepatic dysfunction (fatigue, nausea, anorexia). Toxicity appeared dose related; changes in liver function test results reached statistical significance by the time the dosage reached 1500 mg/day, and 9 of the 12 with substantial hepatotoxicity were taking 2 to 3 g/day. Hepato-toxicity did not develop in any patients taking IR niacin.

EXHIBIT #11

In recent years, numerous case reports have described hepatotoxicity linked to high-dose niacin therapy; almost all the patients were taking SR niacin. Toxicity was noted in some cases in as little as 1 week after initiating therapy, and in others as late as 48 months. Usually, toxicity resolved after drug discontinuation, but in some cases liver dysfunction progressed to stage 3 and 4 encephalopathy, and one patient required liver transplantation. Perhaps even more hepatotoxi- city would have developed in patients in the McKenney study if the trial had continued beyond 5 weeks. Other major side effects reported in the literature include activation of peptic ulcers, hyperuricemia and gout, and impaired glucose tolerance. While McKenney et al. noted no change in uric acid levels, they did see elevations in fasting glucose levels with increasing doses. The elevations were significant in the SR niacin group at doses of 2 g and over. By the end of the trial, six patients with normal glucose levels at baseline (three in each group) had fasting glucose levels above 7.8Ēmmol/L (140 mg/dL). One patient taking IR niacin had a bleeding pep-tic ulcer, apparently from activation of peptic ulcer disease.

A number of products have been implicated in niacin-induced hepatotoxicity, including two prescription products: **Nicobid** from **Rhone-Poulenc Rorer** (Collegeville, PA) and **Slo-Niacin** from **Upsher- Smith** (Minneapolis). Other implicated products include Nature's Plus, Niatrol, Endur-Acin, and generic products from **Rugby Laboratories** (Rockville Center, NY), **Major Pharmaceuticals** (San Diego), and **Goldline Laboratories** (Ft. Lauderdale, FL). According to Goldline, their SR niacin is a generic version of Rhone-Poulenc's Nicobid. Neither Goldline nor Rhone-Poulenc promote their SR niacin for cholesterol reduction. Only two prescription products (both of them IR niacin) are approved for cholesterol reduction: Upsher-Smith's Niacor and Rhone-Poulenc's Nicolar. "All other IR dosage forms and all SR dosage forms are available as nonprescription drugs for the treatment of nicotinic acid deficiencies and are not regulated by the FDA," said McKenney et al. In many published cases, a patient went to the health food store for IR niacin because of the health claims and the price, switched to SR niacin because of side effects associated with IR niacin, and then had to visit the doctor because of symptoms that turned out to be caused by hepatotoxicity. "Given the degree of toxic effects we encountered," said the investigators, "we believe that allowing niacin to remain on the nonprescription market, where it may be used in high doses for cholesterol lowering without proper monitoring by trained health care professionals, presents a potentially serious public health problem."

This study poses some interesting questions. Why was SR niacin more effective than IR niacin in reducing LDL-C? Why was IR niacin more effective for increasing HDL-C? Do phar-macokinetic differences explain the efficacy and toxicity differences? Slower absorption of SR niacin may mean lower peak serum levels, but fewer side effects may mean higher total ingested dose. Increased hepatotoxicity with SR niacin may be due to steadier bathing of liver cells, and the hepato-toxicity may explain the cholesterol reductions.

According to editorialist Louis Lasagna, the FDA has approved niacin for treating hypercholesterolemia, and the National Cholesterol Education Program recommends it for primary prevention. Niacin still has a role in managing dyslipidemia, said Lasagna, "but not on the basis of self-diagnosis and self- treatment." The Medical College of Virgin-ia cholesterol research center routinely evaluates the efficacy and safety of drugs for hypercholesterolemia. "The incidence and severity of adverse reactions experienced with both niacin dosage forms in the present study, but particularly with SR niacin, were much greater than any investigational drug we have evaluated for hypercholesterolemia," concluded McKen-ney et al. "If niacin were being evaluated for efficacy and safety and our experiences were replicated by others, we do not believe that it would be approved by the FDA for use in the management of hypercholesterolemia." (McKenney JM et al. JAMA. 1994;271:672-677. Lasagna L. JAMA. 1994;271:709-710)

US 5126145A

United States P..ent [19]

Evenstad et al.

[11] Patent N..ber: 5,126,145

[45] Date of Patent: Jun. 30, 1992

[54] CONTROLLED RELEASE TABLET CONTAINING WATER SOLUBLE MEDICAMENT

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[58] Field of Search 424/488, 469, 470, 465, 424/489

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Primary Examiner—Thurman K. Page

Assistant Examiner—James M. Spear

[57] ABSTRACT

A sustained or controlled release tablet is disclosed. The tablet comprises a water soluble medicament, a hydroxypropyl methylcellulose having sustaining action, a pharmaceutical binding agent, and a hydrophobic component.

24 Claims, 2 Drawing Sheets

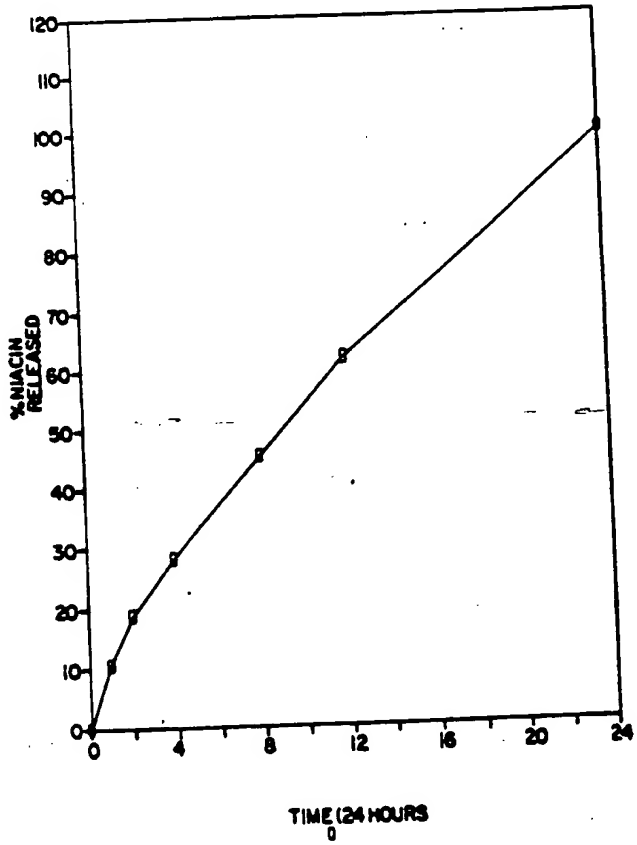


EXHIBIT #12

CONTROLLED RELEASE TABLET CONTAINING WATER SOLUBLE MEDICAMENT

This is a continuation of application Ser. No. 07/337,460, filed Apr. 13, 1989 now abandoned.

This, invention relates to a controlled release tablet comprising hydroxypropyl methylcellulose, a binding agent. an internal hydrophobic component, and water soluble medicament. The tablet can be formed by wet granulation techniques.

BACKGROUND OF THE INVENTION

Sustained or controlled release products for oral administration are known and widely used. Hydroxypropyl methylcellulose has been used in such products. It is believed that hydroxypropyl methylcellulose in such tablets partially hydrates on the tablet surface to form a gel layer. The rate of hydration and gelling of the hydroxypropyl methylcellulose tablet surface affects the drug release from the tablet and contributes significantly to the sustained release aspect of such products.

However, it has been difficult to formulate controlled release tablets of soluble medicaments and hydroxypropyl methylcellulose. First, it has been difficult to achieve the desired dissolution profiles or to control the rate of release of soluble to freely soluble medicaments. This may be due to leaching of the medicament from the tablet before hydration and gelling of the hydroxypropyl methylcellulose occurs. Second, known tableting techniques such as direct compression and granulation may fail when a high proportion of soluble medicament is required regardless of its degree of solubility.

Bead coating technology can be used to form sustained release products. These products typically comprise hard gelatin capsules containing coated beads of medicament. Soluble medicaments are available in controlled release capsules of this type. However, tablets have certain advantages over capsules and these advantages are lost with the use of capsules for sustained release of soluble therapeutic agents.

Tablets have several advantages over capsules. For some drugs, it is recommended that the patient begin taking a smaller dose and gradually over time increase the dose to the desired level. This can help avoid undesirable side effects. Tablets can be preferable to capsules in this regard because a scored tablet easily can be broken to form a smaller dose.

In addition, tableting processes such as wet granulation are generally simpler and less expensive than bead coating and capsule formation. Further, tablets can be safer to use because they may be less subject to tampering.

Accordingly, a need exists for a controlled release product of more soluble medicaments, combining the advantages of hydroxypropyl methylcellulose in sustaining and controlling the release rate, the relative ease and low cost of wet granulation, and the other advantages of the tablet form over capsules.

BRIEF DESCRIPTION OF THE INVENTION

We have discovered a sustained release tablet comprising hydroxypropyl methylcellulose with sustaining properties but negligible binding properties, in an amount effective to produce a desired release rate, sufficient water soluble pharmaceutical binder to permit wet granulation, an amount of internal hydrophobic component effective to permit wet granulation. and a water soluble medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing an average dissolution profile of 750 mg. niacin tablets made in accordance with the invention.

FIG. 2 is a graph comparing the average dissolution profiles of niacin (500 mg) tablets made in accordance with the invention and a commercially available extended-release niacin (500 mg) capsule.

DETAILED DESCRIPTION OF THE E INVENTION

The controlled release tablet includes a medicament and a hydrophillic polymer matrix for achieving controlled or sustained or extended release of the medicament. The tablet can include a high proportion of water soluble medicament and can be prepared by standard wet granulation techniques. A desirable dissolution profile can be achieved. The tablet can be scored to permit easy titration up to the desired dose.

The medicament can be any suitable water soluble therapeutically active material which is commonly administered orally. The medicaments that we believe will benefit most from the invention are those that appear to be too soluble for ready inclusion in an effective controlled release tablet utilizing hydroxypropyl methylcellulose. The solubility of the medicaments could from about 0.1 to 30% (at 25° C.). This includes slightly soluble to freely soluble compounds, according to the definitions provided by Remington Pharmaceutical Sciences.

The minimum amount of medicament or active drug in the tablets of the invention will typically be about 30% by weight based on the weight of the tablet and can range up to about 90%. Within this range, generally it is possible to incorporate a greater amount of a less soluble medicament.

Niacin, with a water solubility of about 1.67 g/100ml (25° C.), is a medicament falling within the scope of the invention. Niacin has the chemical formula $C_6H_5NO_2$ and is also known as nicotinic acid. It is commercially available as fine white crystals or white crystalline powder, from sources such as Lonza and Ashland Chemical. It will typically be present at a level of from 50–85% by weight of the tablet. Other therapeutically active materials suitable for use in the invention include morphine sulfate, chlorpheniramine hydrochloride, pseudoephedrine, codeine sulfate and diltiazem hydrochloride, aspirin, acetaminophen, and naproxen.

The hydrophillic polymer matrix of the tablets of the invention is a dynamic system involving hydroxypropyl methylcellulose wetting, hydration, and dissolution. Other soluble excipients or drugs also wet, dissolve, and diffuse out of the matrix while insoluble materials are held in place until the surrounding polymer/excipient/-drug complex erodes or dissolves away.

The most significant mechanism by which drug release is controlled is through the use of hydroxypropyl methylcellulose. The hydroxypropyl methylcellulose, present throughout the tablet, partially hydrates on the tablet surface to form a gel layer. Overall dissolution rate and drug availability are dependent on the rate of soluble drug diffusion through the wet gel and the rate of tablet erosion. Hydroxypropyl methylcellulose with substitution rates of about 7–30% for the methoxyl group and greater than 7% or about 7–20% for the

hydroxypropoxyl group are prefe..ed for formation f this gel layer. More preferred are substitution rates f 19-30% for the methoxyl gr up and 7-12% for the hydr xypr pyl gr up.

Hydroxypropyl methylcelluloses vary in their viscosity, methoxy content, and hydroxypropoxyl content. Properties also vary. Some have more sustaining properties or the ability to achieve conrolled release of medicaments. Others have good binding properties and are less desirable for sustained properties. By "binding properties" we are referring to the ability to act as a binding agent for tablet production by wet granulation, for example, incorporating the hydroxypropyl methylcellulose into aqueous solution in order to spray onto the dry powders. Hydroxypropyl methylcelluloses with good sustaining properties are too viscous for use as the binder in wet granulation techniques.

The tablets of the invention comprise about 5-30 percent by weight hydroxypropyl methylcellulose with sustaining properties and negligible binding properties. Such hydroxypropyl methylcelluloses generally have a viscosity of no less than about 1000 centipoises.

More typically, the viscosity will be no less than about 4000 cps. For improved performance, the tablet will comprise about 5-20 weight percent, or, more preferably, about 8-12 percent hydroxypropyl methylcellulose with sustaining characteristics.

A preferred hydroxypropyl methylcellulose with sustaining properties is a hydroxypropyl methylcellulose with substitution type 2208, with a nominal viscosity, 2% aqueous, of about 100,000 cps, a methoxyl content of about 19-24%, and a hydroxypropoxyl content of about 7-12%. A "controlled release" grade is preferred, with a particle size where at least 90% passes through a #100 USS mesh screen. A commercially-available hydroxypropyl methylcellulose meeting these specifications is the Methocel K100MCR, from The Dow Chemical Company.

The tablet further comprises or includes about 2-15 weight percent water soluble pharmaceutical binder. The binder or binding agent aids in tablet production by wet granulation, serving as an adhesive and adding strength to the tablet.

Many suitable binders are known. They include polyvinyl pyrollidone, starch, gelatin, sucrose, lactose, methylcellulose, hydroxypropyl methylcellulose, and the like. For good binding action without excess binding agent, we prefer the use of about 2-8% by weight, or more preferably, particularly where the preferred binding agent is used, about 2-5% by weight.

The preferred water soluble pharmaceutical binder for use in this invention is hydroxypropyl methylcellulose having binding properties. Such hydroxypropyl methylcelluloses typically have a much lower viscosity than the hydroxypropyl methylcelluloses that have good sustaining characteristics. Generally, the viscosity of a 2% aqueous solution will be less than about 1000 cps. More typically, it will be less than 100 cps.

A preferred hydroxypropyl methylcellulose for use as a binding agent in the context of the invention has a nominal viscosity, 2% aqueous, of about 15, a methoxy content of about 28-30%, a hydroxypropyl content of about 7-12%, and a particle size of 100% through USS 30 mesh screen and 99% through USS 40 mesh screen. Hydroxypropyl methylcellulose 2910, Methocel E15 from The Dow Chemical Company meets these standards and is a preferred binder.

Other suitable binding hydroxypropyl methylcelluloses include Methocel ESLVP, Methocel E50LVP, and Methocel K3P. The methylcellulose Methocel A1SLVP can also be used.

Another binder we recommend is polyvinyl pyrollidone, also known as polyvidon , povidone, and PVP. Typical properties of commercially available PVP's include density between 1.17 and 1.18 g/ml and an average molecular weight ranging from about 10,000 t 360,000. Generally, the higher molecular weight PVP's would be more suitable for use in this invention. Suppliers include BASF Wyandotte and GAF.

An essential component of the invention is what we refer to as the hydrophobic component. This component permits wet granulation of soluble medicaments with hydroxypropyl methylcellulose where it would not otherwise be easily accomplished using standard wet granulation techniques. In the absence of this component, we have found that the hydroxypropyl methylcellulose/medicament mixture tends to become "doughy" and granules or powder cannot easily be obtained.

The hydrophobic component comprises a wax-like material. The wax-like material comprises a solid generally insoluble substance having a waxy consistency. It should, of course, be ingestible. Many such materials are known and include waxes such as beeswax, carnauba wax, candelilla wax, Japan wax, paraffin, hydrogenated castor oil, higher fatty acids, such as palmitic acid, stearic acid, and myristic acid, esters of such higher fatty acids such as substituted mono-, di-, and tri-glycerides, acetylated monoglycerides, glyceryl monostearate, glyceryl tristearate, cetyl palmitate, glycol stearate, glyceryl tri-myristate, higher fatty alcohols such as cetyl alcohol, stearyl alcohol, and myristyl alcohol, and mixtures thereof.

Two wax-like materials are preferred in view of their ready availability in powdered form, reasonable cost, ease of handling, and their effectiveness in the context of this invention. These waxy materials are hydrogenated vegetable oil and stearic acid. Hydrogenated vegetable oil generally consists mainly of the triglycerides of stearic and palmitic acids, and is readily commercially available. A preferred hydrogenated vegetable oil for use in this invention is available through Edward Mendell, Co., Inc., of N.Y., under the trademark Lubritab ®. The Lubritab ® product has a bulk density of 0.48-0.56 grams per milliliter, a melting point of from 61°-66° C., a saponification value of 188-198, 0.8 maximum unsaponifiable matter, and a typical particle size distribution of 15 percent maximum on 100 mesh USS screen, 35 percent maximum through 200 mesh USS screen. An advantage of this product is its availability in powder form. A similar hydrogenated vegetable oil is available from Durkee, under the trademark Duratex.

Stearic or octadecanoic acid is typically manufactured from fats and oils derived from edible sources, and commercial stearic acid is typically a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid $C_{16}H_{32}O_2$). Stearic acid is available from many chemical suppliers, including Emery Industries and Mallinckrodt, Inc.

The powdered stearic acid NF available from Mallinckrodt contains not less than 40.0 percent $C_{18}H_{36}O_2$ and not less than 40.0 percent $C_{16}H_{32}O_2$; the sum of these tw components is n t less than 90.0 percent. The congealing temperature is not lower than 54°, and the iodine value is not more than 4.

The hydrophobic component should be present in an amount effective to permit wet granulation of the controlled release tablet. Such an amount is commonly 2–20 percent by weight of the tablet depending on the solubility of the medicament. Higher concentrations will be required for more soluble medicaments. Preferably, for good granulating results and sustained release, it will be present at from 5–15 percent of the total tablet weight, or more preferably, 6–12 percent by weight.

Other components commonly used in tablet formation, such as external lubricants, dyes, fillers and extenders, may also be used as desired. External lubricants or tableting aids can include calcium stearate, stearic acid, hydrogenated vegetable oils, talc, corn starch, colloidal silicone dioxide, magnesium stearate, and glyceryl behenate. We have found that a combination of glyceral behenate, magnesium stearate, and colloidal silicon dioxide is particularly effective as a tableting aid.

The external lubricants, typically added to the dried granules before tableting, if used, can be present at up to about 5 percent of the total tablet weight. More preferably, they will be present at 0.5–4 percent, or for improved tableting, 1–3 percent of the tablet weight.

Dyes can, of course, be used for a more pleasing tablet appearance. Many suitable ingestible dyes for tablets are known and are widely available.

Fillers or extenders can be used if needed or desired. When a tablet containing a 250, 500, or 750 mg. dose of niacin is formed, fillers or extenders typically would not be used because the medicament itself supplies sufficient volume to the tablet. However, fillers or extenders may be desirable where a lower dose of medicament is used. Many fillers or extenders are known and are readily available, including calcium sulfate, dicalcium phosphate, tricalcium phosphate, lactose, sucrose, starch dextrose, and microcrystalline cellulose.

The methods of forming the tablets of the invention are typical wet granulation methods, either conventional or fluid bed. A uniform blend of the hydrophobic component (flakes or powder) and dye, if used, is formed. The binding agent is dissolved in water to form a binding agent solution. The hydrophobic component blend, the sustaining hydroxypropyl methylcellulose, and the medicament are granulated using the binding agent solution to a final moisture level of less than about 7 percent, preferably less than about 5 percent. In the conventional process, the granulation is removed from the mixer and oven dried. External lubricating agents are then mixed in and the mixture is tableted. As would be understood by one of skill in the art, fluid bed processing would not require the oven drying step; instead the components would be granulated and dried in one procedure.

Where niacin is the medicament, useful tablets include doses of 250, 500, and 750 mg. High doses such as 750 mg. can cause side effects such as uncomfortable flushing and nausea unless treatment begins with smaller doses. Tablets can be scored to permit easy breakage into smaller doses for titration up to the standard 750 mg. dose given twice daily. Titration, particularly with sustained release tablets, has been shown to help avoid side effects of niacin therapy.

Tablets made according to the invention can have desirable dissolution profiles mimicking zero order absorption characteristics or constant rate of release over time. Niacin tablets in accordance with the invention show dissolution profiles of 10–35% in 2 hours after ingestion, 40–70% in 8 hours, and at least 90% dissolution in 24 hours. Even more preferably, the profile of the niacin tablets is 10–30% release in 2 hours, 40–60% in 8 hours, and complete dissolution in 24 hours, and tablets in accordance with the invention have shown this profile.

The invention will be further understood by reference to the following Examples which include preferred embodiments.

EXAMPLE I

750 mg. niacin tablets were formed having the following components:

	% by Weight	Mg./Tablet
Niacin (Lonza)	73.07	750.0
Hydroxypropyl Methylcellulose 2910 (Methocel E15LV, Dow)	2.50	25.7
Hydroxypropyl Methylcellulose 2208 (Methocel K100MCR, Dow)	9.74	100.0
Hydrogenated Vegetable Oil (Lubritab, Mendell)	11.56	118.7
Glyceryl Behenate (Compritol 888)	0.50	5.1
Magnesium Stearate (Mallinckrodt)	1.50	15.4
FD&C Red #40 Lake Dye (40%) (Colorcon)	0.13	1.3
Colloidal Silicon Dioxide (Syloid 244)	1.00	10.3

To form the tablest, 16 liters of water was heated to 95° C. in a stainless steel container. The Methocel E15LV powder was slowly added while mixing until a homogenous suspension was obtained. The impeller speed was adjusted to avoid excessive air from entering the solution through the vortex.

48 liters of very cold water was slowly added and the mixture was mixed thoroughly until a clear solution was obtained and the temperature was below 20° C. Mixing continued for an additional 20 minutes.

The hydrogenated vegetable oil was sized through a USS No. 16 screen and added to a mixer. The dye was added to the mixer and mixed until the color distribution was uniform, about 5 minutes. The color mix was then transferred to a ribbon blender. The niacin powder was added to the ribbon blender and mixed for about 10 minutes. The Methocel K100MCR was then added and mixed for an additional 10 minutes.

The Methocel E15LV solution was sprayed in and then mixed for 1 minute. The resulting wet granulation was then sized through a USS No. 16 screen.

The sized wet granulation was spread lightly on trays, at approximately 2 kilograms per tray. The granulation was dried in an oven at 230° F. to a moisture content of less than 5 percent. The oven dried granulation was then sized through a USS No. 12 screen. After sizing, the granulation was collected in double poly-lined drums.

Three approximately 200 kilogram batches were formed in the above manner, each utilizing 149.06 kilograms niacin, 3.97 kilograms Methocel E15LV, 19.87 kilograms Methocel K100MCR, 24.84 kilograms Lubritab hydrogenated vegetable oil, and 0.26 kilograms FD&C Red Dye #40 Lake 40% pure dye. These batches were weighed, and combined in a ribbon blender. 3.0 kilograms glyceryl behenate and 3.0 kilograms magnesium stearate were then added to the ribbon blender and the mixture was mixed for 5 minutes.

The resulting product was tableted using a standard rotary press into tablets f 750 milligrams niacin.

EXAMPLE II

750 milligram niacin tablets were formed as foll ws:

Per Part	Milligrams/ Tablet	Kilograms Used
Niacin (Lonza)	750.00	312.500
Hydroxypropyl Methylcellulose 2910 (Methocel E15LV, Dow)	24.00	10.000
Hydroxypropyl Methylcellulose 2208 (Methocel K100MCR, Dow)	94.10	39.200
Hydrogenated Vegetable Oil (Lubritab, Mendell)	62.40	26.00
FD&C Red #40 Lake Dye (40%) (Colorcon)	0.70	0.300

The niacin tablets of Example II were formulated by the fluid bed process. Half of the above quantities were used for the first granulation. In this granulation, 33.000 kilograms deionized water were added to a stainless steel steam kettle and heated to 95° C. While mixing (but avoiding excess foaming), the Methocel E15LV and dye were added to the water. 67.000 kilograms cold deionized water were then added and mixing continued for about 20 minutes. The mixture was cooled to 21° C.

To the fluid bed container were added the niacin. Methocel K100MCR, and Lubritab hydrogenated vegetable oil. These three components were granulated with the Methocel E15LV solution. After exhausting the granulating solution, the material in the fluid bed containers was dried to less than 1% moisture.

The dried material was transferred to clean polylined containers. Using the Sweco Sifter, fitted with a 12 mesh screen, the granulation was sized into clean polylined drums.

A second batch of granulation was formed in an identical manner using the remaining half of the components. The two granulations were then added to a ribbon blender. These components were blended for 5 minutes. 6.000 kilograms magnesium stearate, 2.000 kilogram glyceral behenate, and 4.000 kilograms colloidal silicon dioxide were added to the ribbon blender and mixed for 5 minutes. The material was transferred to clean poly-lined drums and later tableted into tablets containing 750.00 milligrams niacin.

Two other formulations are shown below.

EXAMPLE III

Chemical Name	Milligrams/Tab	Percent
Niacin	750.0	78.125
Methocel E15LV (hydroxypropyl methylcellulose)	24.0	2.50
Methocel K100MCR (hydroxypropyl methylcellulose)	94.1	9.80
Lubritab (hydrogenated vegetable oil)	62.4	6.50
FD&C Red #40 dye	0.7	0.075
Magnesium Stearate	14.4	1.50
Compritol (glyceryl behenate)	4.8	0.50
Syloid 244 (colloidal silicon dioxide)	9.6	1.00

Tablets having the formulation of example III were made using conventional and fluid bed granulating techniques in a production mode.

FIG. 1 sh ws the average dissolution pattern of six tablets having the formula shown in Exampl III.

Tablest were dissolved using a Hanson Dissolution Apparatus with a U.S.P. r tating bracket at 100 rpm in 900 ml. water at 37° C. Samples were taken from each dissolution vessel at 1, 2, 4, 8, 12, and 24 hours, and analyzed by UV for nicotinic acid content. The results show a desirable release pattern.

Chemical Name	Milligrams/Tab	Percent
Niacin	750.0	76.220
Methocel E15LV (hydroxypropyl methylcellulose)	24.0	2.439
Methocel K100MCR (hydroxypropyl methylcellulose)	94.1	9.561
Lubritab (hydrogenated vegetable oil)	86.4	8.780
FD&C Red #40 dye	0.7	0.073
Magnesium Stearate	14.4	1.463
Compritol (glyceryl behenate)	4.8	0.488
Syloid 244 (colloidal silicon dioxide)	9.6	0.976

Tablets having the formulation of Example IV were made using conventional granulating techniques in the laboratory.

Chemical Name	By Weight %	Mg./Tablet
Niacin	73.07	500.00
Methocel E15LV (hydroxypropyl methylcellulose)	2.50	17.11
Methocel K100MCR (hydroxypropyl methylcellulose)	9.74	66.65
Lubritab (hydrogenated vegetable oil)	11.56	79.10
Compritol 888 (glyceryl behenate)	0.50	3.42
Magnesium Stearate	1.50	10.26
FD&C Red #40 dye	0.13	.89
Syloid 244 (colloidal silicon dioxide)	1.00	6.84

Tablets having the composition shown in Example V were made using conventional and fluid bed techniques. The dissolution pattern of tablets made in accordance with the formula of Example V was compared with the dissolution pattern of a typical commercially available extended release capsule, 500 mg. niacin. Six samples of each product were dissolved using a Hanson Dissolution Apparatus with a U.S.P. rotating basket at 100 rpm in 900 ml. of water at 37° C. Samples were taken from each dissolution vessel over a 24-hour period, and analyzed by UV for nicotinic acid content. As shown in FIG. 3, the tablets of the invention followed by similar profile to the commercially available extended release capsules, 500 mg. niacin.

Chemical Name	By Weight % Total	Mg/Tablet
Niacin	73.07	250.00
Methocel E15LV (hydroxypropyl methylcellulose)	2.50	8.55
Methocel K100MCR (hydroxypropyl methylcellulose)	9.74	33.32
Lubritab (hydrogenated vegetable oil)	11.56	39.55
Compritol 888	0.50	1.71

-continued

Chemical Name	By Weight % Total	Mg/Tablet
(glyceryl behenate)	1.50	5.13
Magnesium Stearate	0.13	.45
FD&C Red #40 dye	1.00	3.42
Syloid 244 (colloidal silicon dioxide)		

Tablets having the composition shown in Example VI were made using conventional and fluid bed techniques.

The foregoing description and examples are illustrative of the invention. However, since persons skilled in the art can make various embodiments without departing from the spirit and scope of the invention, the invention is embodied in the claims hereafter appended.

We claim:

1. A controlled release uncoated tablet comprising:

(a) about 5-20 percent by weight hydroxypropyl methylcellulose having a viscosity of about 1000 or greater, a substitution rate for the methoxyl group of about 7-30% and a substitution rate for the hydroxypropoxyl group of about 7-20%;

(b) about 2-8 percent by weight hydroxypropyl methylcellulose having a viscosity of less than about 1000, methyl cellulose, or polyvinyl pyrollidone;

(c) about 5-15 percent by weight hydrogenated vegetable oil or stearic acid; and

(d) a therapeutically active material having a water solubility of about 0.1-30% at normal room temperature;

wherein said tablet has a dissolution profile, with a substantially zero order absorption characteristic, of about 10-35% within 2 hours after ingestion.

2. A controlled release uncoated tablet comprising:

(a) about 5-30 percent by weight hydroxypropyl methylcellulose with sustaining properties;

(b) about 2-15 percent by weight water soluble pharmaceutical binder;

(c) about 2-20 percent by weight hydrophobic component; and

(d) a medicament having a solubility of about 0.1 to 30 wt-% in water;

wherein said tablet has a dissolution profile, with a substantially zero order absorption characteristic, of about 10-35% within 2 hours after ingestion.

3. The controlled release tablet of claim 2 wherein the water soluble medicament comprises niacin and forms about 50-85 percent by weight of the tablet.

4. The controlled release tablet of claim 2 wherein the hydroxypropyl methylcellulose comprises a hydroxypropyl methylcellulose having a nominal viscosity, 2 percent aqueous solution, of about 100,000 cps, a methoxyl content of about 19-24 percent, a hydroxypropoxyl content of about 7-12 percent, and a particle size where at least 90 percent passes through a USS 100 mesh screen.

5. The controlled release tablet of claim 2 wherein the water soluble pharmaceutical binder is selected from the group consisting f hydroxypropyl methylcellulose having binding properties, polyvinyl pyrollid ne, methyl cellulose, gelatin, starch, sucrose, and lactose.

6. The controlled release tablet of claim 5 wherein the water soluble pharmaceutical binder comprises hydroxypr pyl methylcellulose having binding properties.

7. The controlled release tablet of claim 5 wherein the water soluble pharmaceutical binder comprises polyvinyl pyrollidone.

8. The controlled release tablet f claim 6 wherein the hydroxypropyl methylcellulose having binding properties comprises hydroxypropyl methylcellulose having a nominal viscosity, 2 percent aqueous solution, of about 15 cps, a methoxy content of about 28-30 percent, a hydroxypropoxyl content of about 7-12 percent, and a particle size of 100% through a USS No. 30 mesh screen and 99% through a USS No. 40 mesh screen.

9. The controlled release tablet of claim 2 wherein the hydrophobic component comprises a wax-like insoluble material.

10. The controlled release tablet of claim 9 wherein the wax-like insoluble material is selected from the group consisting of hydrogenated vegetable oil and stearic acid:

11. The controlled release tablet of claim 10 wherein the wax-like insoluble material comprises a hydrogenated vegetable oil, the hydrogenated vegetable oil comprising a triglyceride of stearic acid.

12. The controlled release tablet of claim 2 further comprising up to about 5 percent by weight external lubricant.

13. The controlled release tablet of claim 12 wherein the external lubricant comprising glyceryl behenate.

14. The controlled release tablet of claim 13 wherein the external lubricant further comprises magnesium stearate.

15. The controlled release tablet of claim 2 wherein the hydroxypropyl methylcellulose with sustaining properties forms about 5-20 percent by weight of the tablet, the water soluble pharmaceutical binder forms about 2-8 percent by weight of the tablet, and the hydrophobic component forms about 5-15 percent by weight of the tablet.

16. The controlled release tablet of claim 3 wherein the percentage of niacin released in the 2 hours following following ingestion of the tablet is about 10-30 percent by weight.

17. The controlled release tablet of claim 3 wherein the percentage of the niacin released in the 8 hours following ingestion of the tablet is about 40-70 percent by weight.

18. The controlled release tablet of claim 17 wherein at least 90% release of the niacin occurs within 24 hours following ingestion of the tablet.

19. The controlled release tablet of claim 2 wherein the tablet is readily divisible into portions, each portion forming a smaller dose than the dose of the intact tablet.

20. The controlled release tablet of claim 3 wherein the tablet contains about 250 milligrams of niacin.

21. The controlled release tablet of claim 3 wherein the tablet contains about 500 milligrams of niacin.

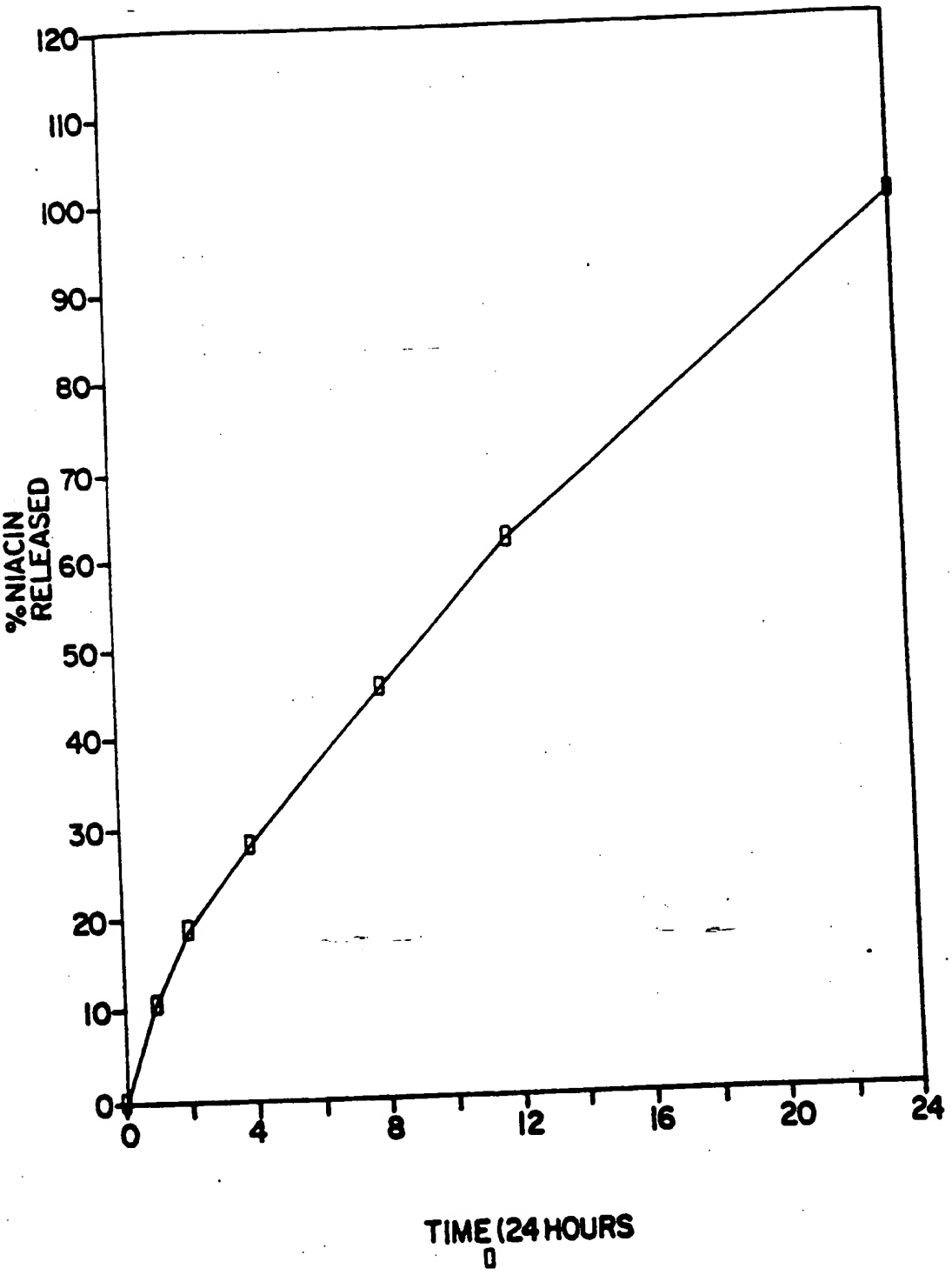
22. The controlled release tablet of claim 3 wherein the tablet contains about 750 milligrams of niacin.

23. The controlled release tablet of claim 1 wherein the therapeutically active material forms from about 30-90% by weight of the tablet.

24. The controlled release tablet of claim 1 wherein the therapeutically active compound comprises niacin and forms from about 50-85 percent by weight of the tablet.

* * * * *

FIG. 1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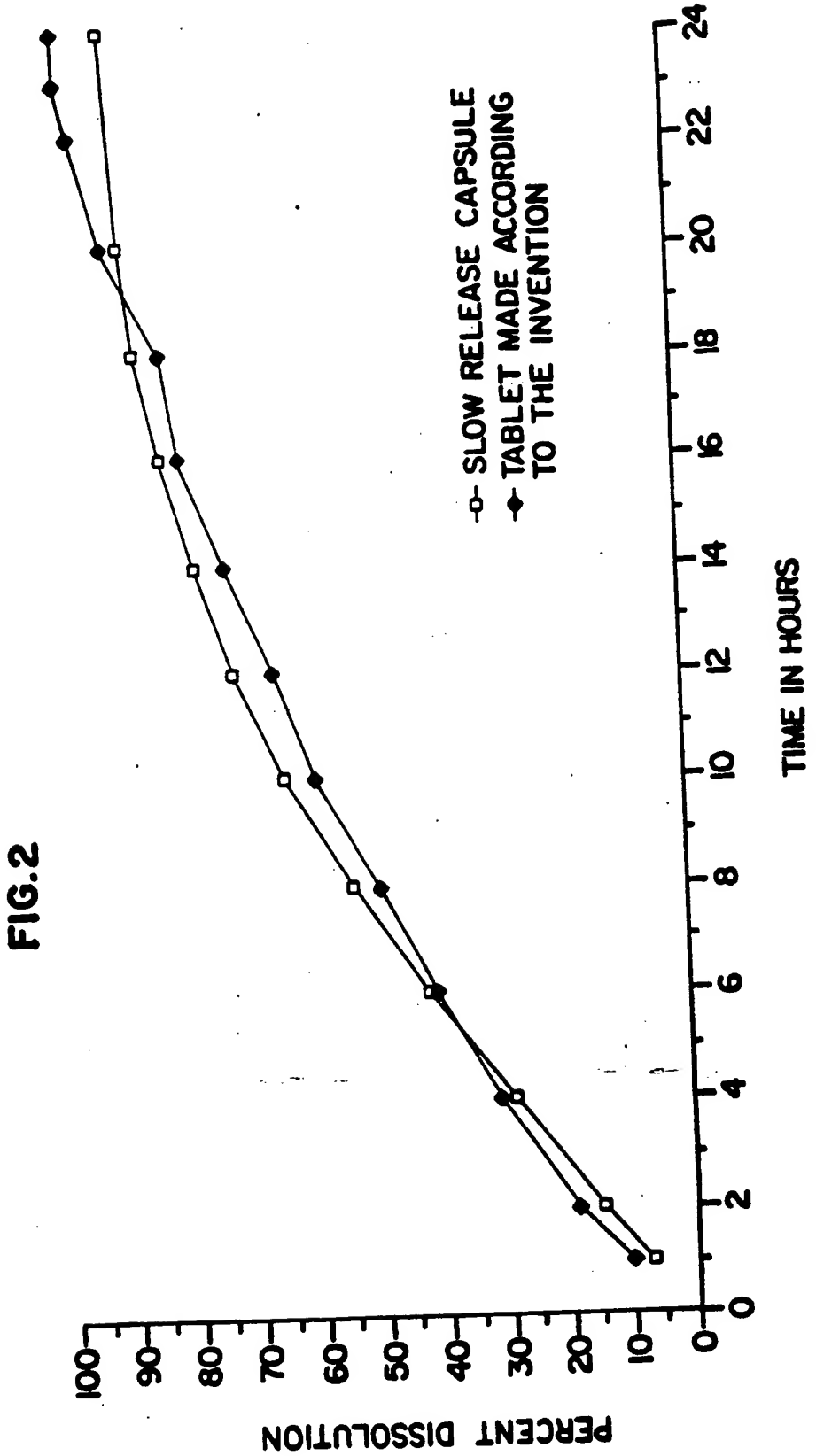
SLOW RELEASE CAPSULE
TABLET MADE ACCORDING TO THE INVENTION
PERCENT DISSOLUTION
TIME IN HOURS
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FIG.2

US005268181A

United States Patent [19]

O'Neill et al.

[11] Patent Number: 5,268,181

[45] Date of Patent: Dec. 7, 1993

[54] **METHOD OF USING NIACIN TO CONTROL NOCTURNAL CHOLESTEROL SYNTHESIS**

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[60] Continuation-in-part of Ser. No. 536,184, Jun. 11, 1990, Pat. No. 5,126,145, which is a division of Ser. No. 337,460, Apr. 13, 1989, abandoned.

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[58] Field of Search 424/464, 465, 474, 476, 424/489; 514/356, 824

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[57] **ABSTRACT**

The invention provides a therapeutic method to treat hyperlipidemia by administering to a human patient a single daily dose of a prolonged release dosage form of niacin, so that nocturnal cholesterol synthesis is effectively suppressed.

11 Claims, No Drawings

EXHIBIT #13

OTHER PUBLICATIONS

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METHOD OF USING NIACIN TO CONTROL NOCTURNAL CHOLESTEROL SYNTHESIS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. patent application Ser. No. 7/536,184, filed Jun. 11, 1990, now U.S. Pat. No. 5,126,145, which is a divisional application of Ser. No. 7/337,460, filed Apr. 13, 1989, abandoned.

BACKGROUND OF THE INVENTION

Guidelines developed by the National Cholesterol Education Program's Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, as reported in *Arch. Intern. Med.*, 148, 36 (1988), identified elevated cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations as the major targets for cholesterol-lowering therapy. The importance of cholesterol reduction in patients with overtly manifest coronary artery disease cannot be overstated, since virtually every major epidemiological study performed to date has shown a significant correlation between the level of serum cholesterol at the time of entry and the risk of subsequent coronary disease. For example, see J. C. Rosa, *Circulation*, 81, 1721 (1990).

The results of 22 randomized cholesterol-lowering clinical trials to reduce the risk of coronary heart disease indicate an average reduction of 23 percent in the risk of non-fatal myocardial infarction and cardiac death in treated compared with control patients. In particular, a 10 percent decrease in the cholesterol level was associated with a reduction of approximately 20 percent in the incidence of new coronary events (S. Yusef et al., *JAMA*, 260, 2259 (1988)).

Present therapeutic guidelines include the recommendation that cholesterol-lowering drugs should be considered when cholesterol and low density lipoprotein-cholesterol (LDL-C) levels remain significantly elevated after six months of appropriate dietary therapy. For example, see "National Education Programs Working Group Report on the Management of Patients With Hypertension and High Blood Cholesterol," *Ann. of Intern. Med.*, 114, 224 (1991).

Niacin is commonly employed to treat hypercholesterolemia because it lowers total serum cholesterol, low density lipoproteins (LDL) and triglycerides, and the attendant risk of cardiovascular disease. In addition, recent observations have shown that niacin is effective to increase low levels of high density lipoproteins (HDL).

Niacin is nicotinic acid (pyridine-3-carboxylic acid). It inhibits lipoprotein synthesis by preventing the secretion of very low density lipoprotein (VLDL) from the liver. Because VLDL is a precursor for the intermediate density lipoproteins (IDL) and LDL, the circulating levels of all of the atherogenic lipoprotein fractions are decreased. In addition, niacin decreases levels of lipoprotein a, which has been associated with a two-fold increase in the relative risk of coronary artery disease. The rate-limiting enzyme in cholesterol biosynthesis is hepatic hydroxymethylglutaryl coenzyme A reductase (HMG-CoA reductase). For example, I. Bjorkhem et al., in *J. Lipid Res.*, 28, 1137 (1987) reported high correlations between the relative concentrations of cholesterol precursors such as free lanosterol and lathostenol, ch lesterol synthesis and the activity f HMG-CoA reductase.

A wide variety of niacin preparations are available from different manufacturers, each having unique bioavailability, pharmokinetic, and safety profiles. In general, lower doses of niacin (1–3 g/day) are used, because they maintain beneficial lipid effects while minimizing adverse side affects. For example, niacin causes prostaglandin-mediated vasodilation, leading to flushing, warm skin, itching rash and tingling. Aspirin is effective in some cases to control these effects, as is gradual dosage escalation. High niacin (4.3 g/day) also causes substantial incidences of gastrointestinal effects, such as constipation, nausea and heartburn.

Although the vasodilatory and gastrointestinal effects of niacin can either be modulated or are absent at dosage levels which are still effective to lower cholesterol, abnormalities in liver function tests have been observed in 19% of patients treated with daily doses of 2.0 g or less of niacin. (J. D. Alderman et al., *Am. J. Cardiol.*, 64, 725 (1989)). For example, serum transaminase can increase to levels at which niacin must be discontinued. Niacin has also produced hepatocellular degeneration and necrosis. The precise mechanism of injury is not known. However, a dose-relationship suggests some intrinsic hepatotoxic potential that is modified by individual patient susceptibility. See, H. J. Zimmerman, in *Hepatotoxicity*, Appleton-Century-Crofts; New York, N.Y. (1978) at pages 510–512.

Therefore, a need exists for a method to administer niacin in doses effective to lower serum lipids, while minimizing or eliminating such dose-limiting side effects.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides an improved therapeutic method to lower serum lipids or lipid components selected from the group consisting of cholesterol, lipoprotein a, total triglycerides and/or low-density lipoprotein-cholesterol (LDL-C) comprising administering to a human in need of such treatment an effective amount of niacin, in a controlled release dosage form. Preferably, the amount of niacin administered is also effective to raise the levels of high density lipoprotein-cholesterol (HDL-C). The niacin is administered in a single dose during a time period during the day when the niacin levels subsequently achieved in vivo are effective to substantially lower the levels of said serum lipids or lipid components which are primarily nocturnally biosynthesized, e.g., between about 8 p.m.–10 p.m. and 6 a.m.–8 a.m. Preferably, the niacin is administered at, or immediately following, the evening meals and before bedtime, i.e., between about 4 p.m. and 8 p.m.

The amount of niacin that is administered is effective to substantially lower at least one serum lipid or lipid component, while not inducing hepatotoxicity at levels which would require the therapy to be discontinued. For example, in accord with the present method, a lowering of cholesterol and LDL-cholesterol of 10–20% each, and an elevation of HDL-C of about 10–20% is believed to be achievable in hypercholesterolemic patients (>250 mg/dl serum) at single total daily doses of niacin (750 mg–2.0 g) that are 25–75% lower than the total spaced daily dose of niacin that would be required to achieve the same efficacy. In other words, a single 750 mg–1.5 g dose of niacin administered between about 4 p.m.–8 p.m. is expected to be as effective as an equal or higher daily dosage of niacin daily, ad-

ministered in two to four divided doses between, i.e., 8 a.m. and 8 p.m.

Furthermore, because at least a maj rity of the niacin is released and metabolized in vivo during a limited preselected period of about 10–12 hours, the liver is not exposed to the constant levels of niacin which result during administration of long-term, spaced daily doses of niacin. Thus, the likelihood that the patient will develop dose-limiting hepatotoxicity is greatly decreased.

The present invention also provides a kit comprising packaging material and a plurality of said controlled-release unit dosage forms of niacin contained within said packaging material, and wherein said packaging material also comprises instruction means, therein or attached thereto, instructing that one or more, e.g., about 1–4, of said unit dosage forms be ingested by a human patient once daily, with the evening meal, or after the evening meal and before bedtime, in order to lower serum lipids or lipid components selected from the group consisting of cholesterol, lipoprotein a, total triglycerides and/or low-density lipoprotein-cholesterol, or to raise high-density lipoprotein cholesterol. Said instruction means can be a printed label or package insert, a cassette tape, a video tape or a magnetic disk.

All percentages are weight percentages of the total tablet weight unless otherwise noted.

DETAILED DESCRIPTION OF THE INVENTION

The ability of the present single daily dose method to lower cholesterol levels achievable heretofore only with higher single or divided doses is believed to be due at least in part to the observation that, in experimental animals, the rate of cholesterol and cholesterol precursor biosynthesis is highest after midnight and lowest during the morning and early afternoon. In the case of humans, T. A. Miettinen, in *J. Lipid Research*, 23, 466 (1982) found that during the night and early morning, the levels of a number of biosynthetic precursors of cholesterol were several times higher than during the daytime. Thus, the peak plasma squalene and methyl sterol levels occurred at midnight and 4 a.m. Since the equivalent circadian rhythm variation in mammals is caused by diurnal changes in the activity of the cholesterol biosynthesis rate-limiting enzyme hydroxymethyl-glutaryl coenzyme A reductase (HMG-CoAR), Mietinen concluded that the variation in precursors which was observed is most likely due to changes in cholesterol synthesis, and that circadian rhythm also regulates human cholesterol production. The accompanying cyclic accumulation of the precursors in the hepatic and intestinal epithelial cells leads to their increased availability for incorporation into blood lipoproteins. Thus, the efficacy of the present invention is grounded on our belief that triglyceride and cholesterol synthesis are predominantly nocturnal events. Thus, while the present method provides little or no niacin in vivo during the daytime, the rate of normal human cholesterol synthesis is believed to be as much as 3–7 times lower during this period.

In order to effectively suppress cholesterol synthesis during a period when the patient would not be readily able or willing to periodically ingest oral niacin, the niacin is preferably administered following the evening meal and prior to bedtime in a single dose. The single dose of niacin preferably is administered via ingestion of ne or more controlled release unit dosage forms, so that effective niacin levels are maintained throughout the night, i.e., during the peak periods of serum lipid/-lipid component biosynthesis.

A useful controlled release tablet is disclosed in commonly assigned Evenstad et al. (U.S. Pat. No. 5,126,145), which is incorporated by reference herein. This tablet comprises, in admixture, about 5–30% high viscosity hydroxypropyl methyl cellulose, about 2–15% of a water-soluble pharmaceutical binder, about 2–20% of a hydrophobic component such as a waxy material, e.g., a fatty acid, and about 30–90% niacin.

More specifically, one such useful controlled release tablet comprises: (a) about 5–20 percent by weight hydroxypropyl methylcellulose having a viscosity of about 10,000 CPS or greater, a substitution rate for the methoxyl group of about 7–30% and a substitution rate for the hydroxypropoxyl group of about 7–20%; (b) about 2–8 percent hydroxypropyl methylcellulose having a viscosity of less than about 100, CPS methyl cellulose, or polyvinyl pyrollidone; (c) about 5–15 percent by weight hydrogenated vegetable oil or stearic acid; and (d) about 30–90% niacin.

High viscosity water-soluble 2-hydroxypropyl methyl cellulose (HPMC) is particularly preferred for use in the present tablets and in the controlled-release tablet coating, due to its sustaining properties with respect to niacin release. A particularly preferred high viscosity HMPC has a nominal viscosity, two percent solution, of about 100,000 CPS, methoxyl content of about 19–24, a hydroxypropyl content of about 7–12 percent, and a particle size where at least 90% passes through a USS 100 mesh screen. (Methocel ® K100MCR). Low viscosity HPMC is preferred as the binder component of the tablet. A particularly preferred low viscosity HPMC has a methoxyl content of about 20–30%, a hydroxylpropyl content of about 7–12 percent, and a particle size where 100% will pass through a USS No. 30 mesh screen and 99% will pass through a USS 40 mesh screen (Methocel ® EIS). In some cases, a portion of the high viscosity HPMC can be replaced by a medium viscosity HPMC, i.e., of about 2000–8,000 cps.

The viscosities reported herein are measured in centipoises (cps or cP), as measured in a 2% by weight aqueous solution of the cellulose either at 20° C. using a rotational viscometer. A "high viscosity" cellulose ether possesses a viscosity of at least about 10,000 cps i.e., about 50,000–100,000 cps. A low-viscosity cellulose ether possesses a viscosity of less than about 100 cps, i.e., about 10–100 cps.

"Water soluble" for purposes of this application means that two grams of powdered cellulose ether can be dispersed by stirring into 100 grams of water at a temperature between 0° C.–100° C. to provide a substantially clear, stable aqueous composition or dispersion (when the dispersion is brought to 20° C.).

Useful hydrophobic components include natural and synthetic waxes such as beeswax, carnauba wax, paraffin, spermaceti, as well as synthetic waxes, hydrogenated vegetable oils, fatty acids, fatty alcohols and the like.

The controlled release niacin tablets preferably can be formulated to contain 250 mg, 500 mg or 750 mg of niacin, and are ingested orally in a number sufficient to provide a total dosage f about 0.750–2.75 g niacin, preferably, about 1.5–2.0 g of niacin.

Preferably, these tablets will release about 10–35 wt-% of the total niacin within about 2 hours in an in

vitro dissolution test, and about 40–70 wt-% of the total niacin in eight hours.

These controlled released tablets can also be coated so as to further prol ng the release of the niacin into the gastrointestinal tract, or to prevent its release into the st mach, in order to prevent or attenuate the gastrointestinal side effects which can accompany niacin administration.

For example, coatings comprising a major portion of a polymeric material having a high degree of swelling on contact with water or other aqueous liquids can be used to further prolong the release of the niacin from the tablets core. Such polymers include, inter alia, cross-linked sodium carboxymethylcellulose (Acdisol-FMC), cross-linked hydroxypropylcellulose, hydroxymethylpropylcellulose, e.g., Methocel ® K15M, Dow Chem. Co., carboxymethylamide, potassium methylacrylate divinylbenzene copolymer, polymethyl methacrylate, cross-linked polyvinylpyrrolidine, high molecular weight polyvinylalcohol, and the like. Hydroxypropylmethyl cellulose is available in a variety of molecular weights/viscosity grades from Dow Chemical Co. under the Methocel ® designation. See also, Alderman (U.S. Pat. No. 4,704,285). These polymers may be dissolved in suitable volatile solvents, along with dyes, lubricants, flavorings and the like, and coated onto the prolonged release tablets, e.g., in amounts equal to 0.1–5% of the total tablet weight, by methods well known to the art. For example, see *Remington's Pharmaceutical Sciences*, A. Osol, ed., Mack Publishing Co., Easton, Pa. (16th ed. 1980) at pages 1585–1593.

Enteric coatings can also be provided to the prolonged release tablets to prevent release of the niacin until the tablet reaches the intestinal tract. Such coatings comprise mixtures of fats and fatty acids, shellac and shellac derivatives and the cellulose acid phthlates, e.g., those having a free carboxyl consent of 9–15%. See, *Remington's* at page 1590, and Zeitova et al. (U.S. Pat. No. 4,432,966), for descriptions of suitable enteric coating compositions.

The invention will be further understood by reference to the following Examples which include preferred embodiments.

EXAMPLE I

750 mg. niacin tablets were formed having the following components:

Ingredient	% by Weight	Mg./Tablet
Niacin (Lonza)	73.07	750.0
Hydroxypropyl Methylcellulose 2910 Methocel ® E15LV, Dow)	2.50	25.7
Hydroxypropyl Methylcellulose 2208 Methocel ® K100MCR, Dow)	9.74	100.0
Hydrogenated Vegetable Oil (Lubritab ®, Mendell)	11.56	118.7
Glyceryl Behenate (Compritol ® 888)	0.50	5.1
Magnesium Stearate (Mallinckrodt)	1.50	15.4
FD&C Red #40 Lake Dye (40%) (Colorcon ®)	0.13	1.3
Colloidal Silicon Dioxide (Syloid ® 244)	1.00	10.3

To form the tablets, 16 liters of water was heated to 95° C. in a stainless steel container. The Methocel ® E15LV powder was slowly added while mixing until h mogen us suspension was obtained. The impeller speed was adjusted to avoid excessive air from entering the solution through the v rtex.

Very cold water, 48 liters of it, was slowly added and the mixture was mixed thoroughly until a clear solution was obtained and the temperature was below 20° C. Mixing continued f r an additional 20 minutes.

The hydrogenated vegetable oil was sized through a USS No. 16 screen and added to a mixer. The dye was added to the mixer and mixed until the color distribution was uniform, about 5 minutes. The color mix was then transferred to a ribbon blender. The niacin powder was added to the ribbon blender and mixed for about 10 minutes. The Methocel ® K1100MCR was then added and mixed for an additional 10 minutes.

The Methocel ® E15LV solution was sprayed in and then mixed for 1 minute. The resulting wet granulation was then sized through a USS No. 16 screen.

The sized wet granulation was spread lightly on trays, at approximately 2 kilograms per tray. The granulation was dried in an oven at 230° F. to a moisture content of less than 5 percent. The oven-dried granulation was then sized through a USS No. 12 screen. After sizing, the granulation was collected in double poly-lined drums.

Three approximately 200 kilogram batches were formed in the above manner, each utilizing 149.06 kilograms niacin, 3.97 kilograms Methocel ® E15LV, 19.87 kilograms Methocel ® K100MCR, 24.84 kilograms Lubritab ® hydrogenated vegetable oil, and 0.26 kilograms FD&C Red Dye #40 Lake 40% pure dye. These batches were weighed, and combined in a ribbon blender. The plasticizer glyceryl behenate (3.0 kilograms) and 3.0 kilograms magnesium stearate were then added to the ribbon blender and the mixture was mixed for 5 minutes. The resulting product was tableted using a standard rotary press into tablets of 750 mgs niacin.

EXAMPLE II

Niacin tablets (750 mg) were formed as follows:

Ingredient	Mg/Tablet	Kilograms
Niacin (Lonza)	750.00	312.5
Hydroxypropyl Methycellulose 2910 Methocel ® E15LV, Dow)	24.00	10.0
Hydroxypropyl Methylcellulose 2208 Methocel ® K100MCR, Dow)	94.10	39.2
Hydrogenated Vegetable Oil (Lubritab ®, Mendell)	62.40	26.0
FD&C Red #40 Lake Dye (40%) (Colorcon)	0.70	0.3

The niacin tablets of Example II were formulated by the fluid bed process. Half of the above quantities were used for the first granulation. In this granulation, 33.000 kilograms deionized water were added to a stainless steel steam kettle and heated to 95° C. While mixing (but avoiding excess foaming), the Methocel ® E15LV and dye were added to the water. Cold deionized water (67.0 kilograms) were then added and mixing continued for about 20 minutes. The mixture was cooled to 21° C.

To the fluid bed container were added the niacin, Methocel ® K100MCR, and Lubritab ® hydrogenated vegetable oil. These three components were granulated with the Methocel ® E15LV solution. After exhausting

the granulating solution, the material in the fluid bed containers was dried to less than 1% moisture.

The dried material was transferred to clean polylined containers. Using the Sweco Sifter, fitted with a 12 mesh screen, the granulation was sized into clean plastic-lined drums.

A second batch of granulation was formed in an identical manner using the remaining half of the components. The two granulations were then added to a ribbon blender. These components were blended for 5 minutes. Magnesium stearate (6.0 kilograms), 2.0 kilograms glycerol behenate, and 4.0 kilograms colloidal silicon dioxide filler were added to the ribbon blender and mixed for 5 minutes. The material was transferred to clean plastic-lined drums and later tableted into tablets containing 750 milligrams niacin.

Two other formulations are shown below.

EXAMPLE III

Ingredient	Milligrams/Tab	Percent
Niacin	750.0	78.125
Methocel ® E15LV (hydroxypropyl methylcellulose)	24.0	2.50
Methocel ® K100MCR (hydroxypropyl methylcellulose)	94.1	9.80
Lubritab ® (hydrogenated vegetable oil)	62.4	6.50
FD&C Red #40 dye	0.7	0.075
Magnesium Stearate	14.4	1.50
Compritol ® (glyceryl behenate)	4.8	0.50
Syloid ® 244 (colloidal silicon dioxide)	9.6	1.00

Tablets having the formulation of Example III were made using conventional and fluid bed granulating techniques in a production mode.

The tablets were dissolved using a Hanson Dissolution Apparatus with a U.S.P. rotating basket at 100 rpm in 900 ml water at 37° C. Samples were taken from each dissolution vessel at 1, 2, 4, 8, 12 and 24 hours, and analyzed by UV for nicotinic acid content. The results show a desirable release pattern.

EXAMPLE IV

Ingredient	Milligrams/Tab	Percent
Niacin	750.0	76.220
Methocel ® E15LV (hydroxypropyl methylcellulose)	24.0	2.439
Methocel ® K100MCR (hydroxypropyl methylcellulose)	94.1	9.561
Lubritab ® (hydrogenated vegetable oil)	86.4	8.780
FD&C Red #40 dye	0.7	0.073
Magnesium Stearate	14.4	1.463
Compritol ® (glyceryl behenate)	4.8	0.488
Syloid ® 244 (colloidal silicon dioxide)	9.6	0.976

Tablets having the formulation of Example IV were made using conventional granulating techniques in the laboratory.

EXAMPLE V

Ingredient	By Weight %	Mg/Tablet
Niacin	73.07	500.00
Methocel ® E15LV (hydroxypropyl methylcellulose)	2.50	17.11
Methocel K100MCR (hydroxypropyl methylcellulose)	9.74	66.65
Lubritab ® (hydrogenated vegetable oil)	11.56	79.10
Compritol ® 888 (glyceryl behenate)	0.50	3.42
Magnesium Stearate	1.50	10.26
FD&C Red #40 dye	0.13	.89
Syloid ® 244 (colloidal silicon dioxide)	1.00	6.84

Tablets having the composition shown in Example V were made using conventional and fluid bed techniques.

EXAMPLE VI

Ingredient	By Weight % Total	Mg/Tablet
Niacin	73.07	250.00
Methocel ® E15LV (hydroxypropyl methylcellulose)	2.50	8.55
Methocel ® K100MCR (hydroxypropyl methylcellulose)	9.74	33.32
Lubritab ® (hydrogenated vegetable oil)	11.56	39.55
Compritol ® 888 (glyceryl behenate)	0.50	1.71
Magnesium Stearate	1.50	5.13
FD&C Red #40 dye	0.13	.45
Syloid ® 244 (colloidal silicon dioxide)	1.00	3.42

Tablets having the composition shown in Example V were made using conventional and fluid bed techniques.

Tablets having the composition shown in Example VI were made using conventional and fluid bed techniques.

EXAMPLE VIII

Projected Clinical Trial

The primary objective of this study will be to compare the efficacy of a single dose slow-release niacin preparation in the reduction of LDL cholesterol with the efficacy of the same total dose given twice daily (b.i.d.). A placebo group will also be included. Clinical efficacy will be considered to be a 15% or greater decrease in LDL from baseline values. Distribution of patients with fractional reductions will also be evaluated. Secondary efficacy parameters will be changes in triglycerides, HDL cholesterol and apolipoprotein levels, and adverse reactions, particularly hepatotoxicity.

For initial inclusion, a patient must exhibit hypercholesterolemia (total cholesterol ≧240 mg/dL) at screening, have normal liver function test results (bilirubin, SGOT and alkaline phosphatase each no more than 1.5 times normal). Only males and non-pregnant, non-lactating females, 18 to 75 years of age will be included, and sexually active females must be either at least one year postmenopausal, sterile, have had an intrauterine device (IUD) in place for greater than two months or be using an approval oral contraceptive. In order to quality for the treatment phase, patients must have a mean LDL cholesterol level f ≧160 mg/dL for the last two baseline visits.

This is a double-blind, placebo controlled, randomized, parallel study. For each subject group, it inv lves

an eight-week baseline period, a one-week "low-dose" period, a dose titrati n period f f ur weeks and f ur weeks of treatment at the highest tolerated dose f niacin (efficacy phase). Following four weeks of treatment at the highest tolerated dose, there will be an additional nine-week foll w-up period for those patients who respond to and tolerate either niacin treatment. Placebo-treated patients, or patients who have failed to respond to the niacin treatment will not participate in the follow-up portion but will receive appropriate treatment from their physician.

Hyperlipidemic patients not already on an appropriate diet will be stabilized on the American Heart Association Step 1 Diet (or equivalent) during the eight-week baseline period during which time lipid profiles will be determined at weeks 0, 4, 6 and 8. Patients will receive placebo tablets from week 4 (Visit 2). Baseline for patients already stabilized on a diet can be reduced to four weeks. All patients will receive placebo treatment for four weeks prior to entry into the Treatment Phase of the study.

The niacin given to the b.i.d. group was in the form of controlled release 250 mg, 500 mg and 750 mg tablets of Examples VI, V and I, respectively, hereinabove. The niacin given to the single dose groups was in also in the form of the 250 mg, 500 mg and 750 mg controlled release tablets.

At the end of the baseline period, patients who qualify for randomization into the treatment period will be assigned to either single dose niacin, b.i.d. niacin, or placebo treatment. Niacin dosage will be titrated to the highest tolerated dose (maximum 1.5 gm per day), and will remain on that dose for the four-week treatment period. Patient groups will receive niacin 250 mg b.i.d. dosed at breakfast and at the evening meal for one week, or 500 mg to be taken in a single dose with the evening meal. Then the dose will be increased to 500 mg b.i.d. or 1.0 g in one dose at the daily meal. Patients who cannot tolerate 500 mg b.i.d. for at least four weeks will be dropped from the study. After four weeks, the dose for those patients who do tolerate 500 mg b.i.d. will be increased to 750 mg b.i.d. or 1.5 g taken as two 750 mg tablets at the evening meal, for the next four weeks.

If necessary, during the first nine weeks of treatment, the dose may be reduced to 500 mg b.i.d. or 1.0 g in the single dose group, and the patient will be treated at the lower dose for at least nine consecutive weeks. Whenever possible, all patients who respond to the niacin treatment and tolerate it well will remain on their highest tolerated dose for an additional nine-week follow-up period. During the treatment period, fasting lipid profiles will be performed at each visit (the 3rd, 6th and 9th week of each phase).

At the conclusion of the study, the patients in the b.i.d. group and in the single dose group are found to exhibit substantially equivalent lowering of their LDL-C from baseline (avg.=12.5%), while the HDL-C levels of both groups also increase by an equivalent amount (avg.=22.5%). Significantly, 20% (n=20) of the b.i.d. niacin group exhibit at least one abnormal liver function test result (>1.5 times normal level), while only 2.5 (n=2) of the single dose niacin group exhibit an abnormal liver test result.

Thus, this trial demonstrates that a combination of single dose, prolonged release niacin in equivalent in its hypolipidemic effects to the same dose of controlled-release niacin given b.i.d., while exhibiting substantially fewer liver abnormalities.

All publications, patents and patent applications are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

It will be apparent to one of ordinary skill in the art that many changes and modifications can be made in the invention without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A therapeutic method for lowering serum lipids or lipid components consisting essentially of administering to a human in need of such treatment an amount of a single daily dose of niacin which is effective to lower the nocturnal levels of a serum lipid or lipid component selected from the group consisting of total serum cholesterol, total triglycerides, lipoprotein a and low-density lipoprotein-cholesterol (LDL-C), wherein said dose of niacin is administered by ingestion of at least one controlled release tablet comprising, in admixture, about 5-30 % high viscosity hydroxypropyl methyl cellulose having a nominal viscosity, 2% aqueous solution, of at least about 10,000 cps, a methoxyl content of about 7-30% and a hydroxypropyl content of about 7-20%, about 2-15% of a water-soluble pharmaceutical binder, about 2-20% of a hydrophobic component and about 30-90% niacin.

2. The method of claim 1 wherein said treatment also raises the levels of high density lipoprotein cholesterol (HDL-C).

3. The method of claim 1 wherein the single dose of niacin is administered with the evening meal of said human or after the evening meal of said human but before bedtime.

4. The method of claim 1 wherein the tablet further comprises a coating comprising a water-swellable polymer.

5. The method of claim 4 wherein the coating of the water-swellable polymer is overcoated with an enteric coating.

6. The method of claim 1 wherein the tablet comprises about 50-85% niacin.

7. The method of claim 1 wherein the hydrophobic component comprises a wax.

8. The method of claim 1 wherein the hydroxypropyl methyl cellulose has a nominal viscosity, 2 percent aqueous solution, of about 50,000-100,000 cps.

9. The method of claim 8 wherein the hydroxypropylmethyl cellulose has a nominal viscosity, two percent solution, of about 100,000 cps, a methoxyl content of about 19-24%, a hydroxypropyl content of about 7-12 percent, and a particle size where at least ninety percent passes through a USS 100 mesh screen.

10. The method of claim 1 wherein the water-soluble pharmaceutical binder is selected form the group consisting low-viscosity hydroxypropyl methylcellulose which has a nominal viscosity, two percent solution, of less than about 100 cps, polyvinyl pyrollidone, methyl cellulose, gelatin, starch, sucrose and lactose.

11. The method of claim 1 wherein the tablet is a 250 mg tablet, a 500 mg tablet, a 750 mg tablet or mixtures thereof.

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